UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF INDIANA
INDIANAPOLIS DIVISION

ALCON RESEARCH, LTD. (f/k/a ALCON MANUFACTURING, LTD.), ALCON LABORATORIES, INC., and KYOWA HAKKO KIRIN CO., LTD., Plaintiffs,	)	
vs.	)	1:06-cv-1642-RLY-TAB (Consolidated)
APOTEX INC. and APOTEX CORP., Defendants.	)	

FINDINGS OF FACT AND CONCLUSIONS OF LAW

Plaintiffs, Alcon Research, Ltd. (f/k/a Alcon Manufacturing, Ltd.), Alcon Laboratories, Inc. (collectively "Alcon"), and Kyowa Hakko Kirin Co. Ltd. (f/k/a Kyowa Hakko Kogyo Co. Ltd.) ("Kyowa") (collectively "Plaintiffs"), filed suit against the Defendants, Apotex, Inc. and Apotex Corp. (collectively "Apotex" or "Defendants"), for infringement of United States Patent No. 5,641,805 ("the '805 patent"). The parties tried this case before the court from April 26, 2010, through May 7, 2010. Following the trial, the parties filed proposed findings of fact and conclusions of law. The parties presented their final arguments to the court on August 3, 2010.

Being duly advised, the court finds that Plaintiffs have proven, by a preponderance of the evidence, that the Defendants' generic equivalent of Plaintiffs' patented allergy topical ocular medication, Patanol®, infringed claims 1-8 of the '805 patent. The court finds that Defendants have failed to prove by clear and convincing evidence that claims 1-8 of the '805 patent are invalid as obvious under 35 U.S.C. § 103, as anticipated under 35 U.S.C. § 102, and for lack of written description under 35 U.S.C. § 112. The court further finds that Defendants have failed to prove by clear and convincing evidence that the '805 patent is unenforceable due to inequitable conduct.

The court now issues its findings of fact and conclusions of law pursuant to Federal Rule of Civil Procedure 52(a):

FINDINGS OF FACT[1]

I. The Parties

1. Alcon Research, Ltd. (f/k/a Alcon Manufacturing, Ltd.) is a corporation organized and existing under the laws of the State of Delaware, having its corporate offices and principal place of business at 6201 South Freeway, Fort Worth, Texas 76134. (Docket # 173, Stipulation ¶ 1).

2. Alcon Laboratories, Inc. is a corporation organized and existing under the laws of the State of Delaware, having its corporate offices and principal place of business at 6201 South Freeway, Fort Worth, Texas 76134. (Docket # 173, Stipulation ¶ 2).

3. Kyowa Hakko Kirin Co., Ltd. (f/k/a Kyowa Hakko Kogyo Co., Ltd.) is a corporation organized and existing under the laws of Japan, having its principal place of business at 1-6-1 Ohtemachi, Chiyoda-ku, Tokyo 100-8185, Japan. (Docket # 173, Stipulation ¶ 3).

---

[1] Citations to the trial transcript will be "[witness name] Tr." followed by "[transcript page: line];" citations to the deposition testimony submitted by the parties will be "[witness name] Dep." followed by "[dep. page: line]"; citations to the trial exhibits will be "TX" followed by the exhibit number; citations to Plaintiffs' demonstrative exhibits will be "AA" followed by the exhibit number; citations to the parties' pre-trial stipulations, Docket Nos. 173, 179, and 204, which are part of the trial record, will be "[Docket No.], Stipulation" followed by the paragraph number; and citations to any other document on the court's docket will be "[Docket No.]" followed by the title of the document.

4. Apotex, Inc. is a corporation organized and existing under the laws of Canada, having its principal place of business at 150 Signet Dr., Weston, Ontario M9L 1T9. (Docket # 173, Stipulation ¶ 4).

5. Apotex Corp. is a corporation organized and existing under the laws of the State of Delaware, having its principal place of business at 2400 North Commerce Parkway, Suite 400, Weston, Florida 33326. (Docket # 173, Stipulation ¶ 5).

6. Alcon Laboratories, Inc. holds the approved New Drug Application ("ANDA"), # 20-688, for Patanol® ophthalmic solution. The NDA was approved on December 18, 1996. (Docket # 173, Stipulation ¶ 6).

7. On June 6, 1995, Alcon Laboratories, Inc. and Kyowa Hakko Kogyo Co. filed United States Patent Application # 08/469,729 (the "'729 application"), naming John Yanni, Stella Robertson, Eiji Hayakawa, and Masashi Nakakura as inventors. (Docket # 173, Stipulation ¶ 7).

8. The '729 application issued on June 24, 1997, as the '805 patent, entitled "Topical Ophthalmic Formulations for Treating Allergic Eye Diseases." Alcon Laboratories, Inc. and Kyowa Hakko Kogyo Co. Ltd., were the original assignees of the '805 patent. (Docket # 173, Stipulation ¶ 7).

9. Alcon Laboratories, Inc.'s interest in the '805 patent has been subsequently assigned to Alcon Research, Ltd. Alcon Laboratories, Inc. sells drug products covered by the '805 patent under the trademark Patanol® pursuant to an ANDA held by Alcon Laboratories, Inc. and approved by the Food and Drug

Administration ("FDA"). (Docket # 173, Stipulation ¶ 8).

10. Kyowa Hakko Kogyo Co., Ltd.'s interest in the '805 patent has been subsequently assigned to Kyowa Hakko Kirin Co., Ltd. (Docket # 173, Stipulation ¶ 9).

11. Patanol® is approved for the treatment of the signs and symptoms of allergic conjunctivitis. TX 131 at NDA000008; NDA000029 (showing approved indications on Patanol®'s label). The active ingredient of Patanol® is olopatadine hydrochloride. The concentration of Patanol® is 1 mg/mL, or 0.1% w/v. (Docket # 173, Stipulation ¶ 10).

12. Apotex is the owner of ANDA # 78-350, which was submitted to the FDA under section 505(j) of the Federal Food, Drug and Cosmetic Act ("FDCA"), and seeks approval to engage in the commercial manufacture, use, and sale of a generic olopatadine hydrochloride product ("Apotex's product") prior to the expiration of the '805 patent. (Docket # 173, Stipulation ¶ 13).

13. By letter dated October 2, 2006 (the "Notice Letter"), Apotex notified Plaintiffs that Apotex had submitted ANDA # 78-350 to the FDA. (Answer ¶ 16). In the Notice Letter, Apotex notified Plaintiffs that, as part of its ANDA, it had filed a certification of the type described in section 505(j)(2)(A)(vii)(IV) of the FDCA ("Paragraph IV" certification). (Answer ¶ 18); TX 131 at ANDA000043 (Paragraph IV certification statement).

14. On November 15, 2006, Plaintiffs brought suit against Apotex, asserting infringement of the '805 patent, arising out of Apotex's filing of ANDA # 78-350.

(Docket # 1, Complaint).

15. Jurisdiction and venue are proper in this district pursuant to 28 U.S.C. §§ 1331, 1338(a), 1391, and 1400(b). (Docket # 21, Answer ¶ 8; Docket # 35, Entry on Defendants' Motion to Transfer at 3 (no dispute between parties that the Southern District of Indiana is a proper venue)).

II. The Science of Allergy and the Invention of Patanol®

A. The Human Eye, the Conjunctiva, and Mast Cells

16. Mast cells are specialized cells that exist in many places throughout the body, including the eye, and are the primary cells involved in allergic reactions. (Kaliner Tr. 466:8-469:2, 476:3-24, 484:15-485:3; Bielory Tr. 1033:1-8, 1051:8-16; 1053:8-16).

17. The mast cells in the eye are located in the conjunctiva, which is the mucous membrane that lines the inner surface of the eyelids and the sclera on the front of the eyeball. (Yanni Tr. 113:24-114:20; AA-026.02; AA-027; Kaliner Tr. 459:25-460:3). The conjunctiva does not cover the tissues responsible for sight, including the cornea, lens, and retina. (Yanni Tr. 114:21-115:3; Kaliner Tr. 460:12-18; AA-027).

18. Like all mucous membranes, the conjunctiva is designed to keep things that are meant to be in the body in, and to prevent foreign matter from entering the body. The secretion of mucous on the surface of the membrane removes and flushes foreign objects from the surface of the membrane and protects the surface.

(Kaliner Tr. 461:10-463:16; AA-33; AA-71).

19. The mast cells do not reside on the very surface of the eye. Within the conjunctiva, the epithelial goblet cells are located closest to the surface. (Kaliner Tr. 462:20-463:16, 464:15-466:7; AA-071; AA-033). Below the epithelial layer is a basement membrane. (Kaliner Tr. 464:15-466:7; AA-033; AA-071). Below the basement membrane is an area referred to as either the substantia or lamina propria. (Kaliner Tr. 464:15-466:7; AA-033; AA-071). The mast cells in the eye are located below the basement membrane in the substantia propria. (Kaliner Tr. 465:2-13; AA-071).

20. Mast cells contain granules, each of which contain pre-formed mediators. (Kaliner Tr. 467:10-468:15; AA-30; AA-32). Mediators are chemicals that, if released from the mast cells, have some effect on receptors located in the surrounding tissue. (Kaliner Tr. 467:10-468:15; AA-093). Each granule contains up to 25 different types of chemical mediators. (Kaliner Tr. 467:10-468:15; AA-093).

21. Adjacent to the conjunctiva is the conjunctival sac, which contains an extremely small amount of fluid that keeps the tissues moist. (Kaliner Tr. 460:19-461:6; AA-027).

B. The Allergic Cascade

1. Mediator Release Through Degranulation

22. The allergic response is a mechanism that the human body uses to attempt to expel something it recognizes as a foreign invading substance. (Yanni Tr. 119:16-

120:4).

23. In the eye, the most common type of allergic disease is called allergic conjunctivitis. (Kaliner Tr. 507:2-13).

24. In general, an allergic reaction can occur in the sensitized human being upon exposure to an antigen. An antigen is a substance that has the ability to trigger an immunologic reaction, such as the production of antibodies. (Yanni Tr. 116:18-118:14; Kaliner Tr. 470:2-22).

25. Common antigens include substances such as cat dander, pollen, and ragweed. (Yanni Tr. 117:10-118:6; Kaliner Tr. 470:2-22).

26. Exposure occurs when an antigen, like pollen, comes into contact with the outer epithelial layer of the conjunctiva. Small proteins break off from the pollen grain and move through the epithelium, through the basement membrane, and into the substantia or lamina propria where the mast cells are located. (Kaliner Tr. 465:2-13).

27. In the portion of the human population that is genetically predisposed to do so, exposure over a period of time to certain antigens through the mucous membranes causes the body to produce antibodies. The antibodies bind to the surface of the mast cells. (Yanni Tr. 117:10-118:14; Kaliner Tr. 470:2-471:13; AA-19.01-.03).

28. When antibodies bind to the surface of mast cells, they confer sensitivity to these cells. When those cells are subsequently exposed to the antigen, the antigen binds to the antibodies on the surface of the cells, causing them to secrete the chemical

mediators within them. This process of releasing the pre-formed mediators is referred to as degranulation. (Yanni Tr. 118:5-119:6; Kaliner Tr. 471:8-472:10; AA-19.04-.07).

29. The pre-formed chemical mediators found in mast cells vary depending on the type of mast cell, and may include histamine, heparin, tryptase, chymase, and other chemicals. (Yanni Tr. 116:17-117:9; Kaliner Tr. 474:3-16; AA-93).

2. Mediator Production in the "Late Phase" of the Allergic Cascade

30. Mast cells also have the ability to synthesize and release other chemical mediators and cytokines that are synthesized and released after the release of pre-formed mediators, which occurs in what is called the late phase of the allergic reaction. (Kaliner Tr. 473:5-18). The late phase reaction is an inflammatory response in which white blood cells, called eosinophils, are attracted to the eye and make the eye quite irritable for an extended period of time. (Kaliner Tr. 473:5-18).

3. Signs and Symptoms of Allergy

31. Within the surrounding tissues of the eye, there are different types of receptors that correspond to the different mediators released from the mast cells. (Yanni Tr. 118:24-119:6; Kaliner Tr. 471:22-473:4; AA-19.01; AA-19.07-.09).

32. After mediators and cytokines are released from mast cells, they bind to the corresponding receptors and trigger physiological reactions in the body that are commonly identified as allergic symptoms – redness, itching, swelling, watering eyes, running nose, etc. (Yanni Tr. 119:7-15; Kaliner Tr. 471:22-473:4; AA-

19.09; AA-20).

C. Treating Allergic Eye Disease

33. Patients with allergic conditions are treated by interfering with the allergic cascade at one or more points in the process. (Kaliner Tr. 498:15-500:5).

34. In 1995, there were three primary classes of compounds used to treat allergic conjunctivitis: (1) antihistamines; (2) antihistamines combined with vasoconstrictors; and (3) cromolyn sodium, a compound that was reported to be a mast cell stabilizer based on animal testing. (Yanni Tr. 120:5-121:5).

1. Antihistamines (With or Without Vasoconstrictors)

a. Antihistamines Have Limited Effect

35. A standard antihistamine interferes with the allergic cascade toward the end of the process by preventing histamine that has been released from mast cells from binding to particular histamine receptor sites by blocking those receptors. (Kaliner Tr. 496:19-498:8; AA-22.01-.03; AA-22.06; AA-22.08).

36. If an antihistamine is administered after histamine has already been released, the antihistamine can displace histamine from a histamine receptor and replace it, which stops the allergic symptoms caused by that mediator. (Yanni Tr. 122:19-123:25; Kaliner Tr. 496:19-498:8; AA-22.05a; AA-22.05b).

37. Antihistamines are only effective in relieving symptoms caused by histamine binding to those H_1 receptors and do not have any effect on signs or symptoms caused by mediators other than histamine that are released from the mast cell.

(Yanni Tr. 124:1-8; Kaliner Tr. 498:15-499:4).

38. Antihistamines also do not have any effect on the symptoms caused by the late phase of the allergic reaction. (Kaliner Tr. 498:15-499:20).

b. Many Oral Antihistamines Cannot Be Made Into Topical Ophthalmic Preparations

39. Oral antihistamines have been on the market since around 1950 and were the first treatment used for allergic eye disease. (Kaliner Tr. 493:7-22).

40. Not all antihistamines can be used topically on the eye, (Bielory Tr. 1230:10-12), because of the challenges in turning an orally administered systemic antihistamine into a topically applied antihistamine. (Kaliner Tr. 494:21-495:12). In fact, none of the best-selling systemic antihistamines on the market – Claritin, Zyrtec, and Allegra – have been formulated as eye drops despite attempts to do so. (Kaliner Tr. 494:21-495:12; Abelson Tr. 1898:20-1901:3).

41. In 1995, the person of ordinary skill in the art (or "POOS") understood that there were significant barriers to adapting a known systemic antihistamine for topical use in the eye. (Kaliner Tr. 493:15-495:12). Indeed, both sides' experts agree that some antihistamines are simply not bioavailable when applied topically to the eye, others cannot be formulated in an eye drop that is tolerable in the eye or are not sufficiently soluble, and some antihistamines that are systemically effective exhibit unacceptable side effects when applied directly to the eye. (Kaliner Tr. 493:15-495:12; Bielory Tr. 1230:13-21; Abelson Tr. 1901:7-1902:2).

42. In 1995, the POOS would not have been able to have a reasonable expectation regarding whether an antihistamine that was effective when given orally could have been formulated as an effective topical product. (Abelson Tr. 1900:16-1901:3; Kaliner Tr. 495:13-496:14).

43. Furthermore, in 1995, the POOS would not have been able to predict whether an antihistamine that was effective when given orally would be bioavailable and pharmacologically effective if applied topically to the eye. (Kaliner Tr. 496:6-18).

2. Antihistamines with Vasoconstrictors

44. Vasoconstrictors (also called decongestants) have also been used to treat allergic eye disease. (Kaliner Tr. 500:6-501:2). Decongestants act only on the end organ response to the allergic reaction by shrinking the blood vessels. (Kaliner Tr. 500:6-501:2). Decongestants have a limited effect and can lead to a rebound effect where the congestion becomes worse after use is discontinued. (Kaliner Tr. 500:6-501:2).

45. Combinations of antihistamines and vasoconstrictors have been used to try to block the itching caused by histamine and the redness caused by vasodilation. (Kaliner Tr. 501:3-9). These products do not work nearly as well as prescription products. (Kaliner Tr. 501:10-16).

3. Mast Cell Stabilizers

46. A more effective way to provide relief to the patient is to significantly reduce or prevent mast cell mediator release. This is referred to as stabilizing the mast cell

or mast cell stabilization. Mast cell stabilization shuts down the start of the allergic cascade and significantly reduces or prevents all allergic symptoms. (Yanni Tr. 124:11-125:19; Kaliner Tr. 499:21-500:5).

47. A mast cell stabilizer will prevent or inhibit all of the mediators – of which there are many – from being released from the mast cells. (Kaliner Tr. 499:21-500:5; 474:3-16; AA-93). There are not individual mast cells, or even granules within a mast cell, that contain one type of mediator; instead each granule within each mast cell contains a host of different chemical mediators. (Kaliner Tr. 467:10-468:15). It is not possible to selectively inhibit the release of histamine from a mast cell but not inhibit the release of other mediators. (Yanni Tr. 125:11-19).

4. The Search for an Effective Mast Cell Stabilizer

48. As the role of the mast cell in the allergic cascade became widely known in the field, skilled practitioners realized the potential advantages of preventing mediator release through mast cell stabilization. (Kaliner Tr. 501:17-502:3).

a. Early Experience with Cromolyn

49. In the 1970s, researchers believed that cromolyn was a mast cell stabilizer based on testing in animal mast cells. Cromolyn was thus classified as a mast cell stabilizer because it appeared to stabilize rat peritoneal mast cells, but it subsequently was shown not to effectively stabilize mast cells in any human tissue. (Kaliner Tr. 478:12-480:10).

50. Cromolyn was approved to treat a particular type of conjunctivitis called vernal

keratoconjunctivitis, which is a special type of conjunctivitis in the eye that is not mast cell dependent and is therefore not treated through mast cell stabilization. (Yanni Tr. 121:14-23; Kaliner Tr. 507:2-13).

51. Clinical studies examining cromolyn used in the human eye found that cromolyn had marginal clinical efficacy for treating allergic conjunctivitis when compared to placebo. (TX 716 at 1027; Kaliner Tr. 508:15-25).

52. By 1995, scientists in the allergy field did not consider cromolyn to be a mast cell stabilizer in the human eye and the POOS would have known that it was not. (Kaliner Tr. 507:2-509:14; Yanni Tr. 121:11-13). The mechanism of action of cromolyn is still not known. (Yanni Tr. 121:6-10).

b. Scientists Looked for Years for an Effective Mast Cell Stabilizer

53. For years, scientists in the area searched for a mast cell stabilizer that would be effective in various human mast cell populations, including the eye, and failed. (Kaliner Tr. 503:24-504:25; Abelson Tr. 1736:10-17).

54. The search for mast cell stabilizers that are effective in humans has involved many companies, compounds, and dollars. (Kaliner Tr. 503:24-504:25). The therapeutic benefits of an effective human mast cell stabilizer to treat allergic eye disease led researchers and drug companies to actively pursue that development. (Kaliner Tr. 503:24-504:25).

55. In 1995, there was a long felt need for a human conjunctival mast cell stabilizer

that had not been met. (Kaliner Tr. 509:15-23; Abelson Tr. 1736:10-17).

56. Despite the efforts of many companies researching many compounds, nobody found an effective mast cell stabilizer for the human eye prior to the invention of the ‘805 patent. (Kaliner Tr. 503:8-23; Abelson Tr. 1736:10-17).

5. Compounds Referred to as “Anti-Allergic”

57. There is a difference between generally impeding an allergic response and inhibiting the release of mediators from a mast cell. (Kaliner Tr. 474:17-475:5). Just because a drug has an anti-allergic response does not mean that it is a mast cell stabilizer, and the POOS would not have had a reasonable expectation that merely because a compound was effective as an “anti-allergic” that it would be a mast cell stabilizer. (Kaliner Tr. 474:17-475:5; Abelson Tr. 1749:16-1751:17). Inhibition of an allergic reaction, standing alone, does not indicate by what mechanism of action a compound is inhibiting the allergic reaction. (Yanni Tr. 127:9-128:12; Kaliner Tr. 474:17-475:5).

58. The term “anti-allergic” is frequently used to describe a drug that interferes with some point in the allergic cascade, although, depending on the context, that term can have multiple meanings. (Kaliner Tr. 474:17-475:5). In its most common usage, “anti-allergic” describes any drug that interferes with any point of the allergic cascade, including antihistamines, mast cell stabilizers, and drugs that interfere with or block the effects of any other mediator. (Kaliner Tr. 474:17-475:5). In a less common usage, the term “anti-allergic” can be used to indicate a

drug that reduces the allergic reaction by stabilizing the mast cells by blocking histamine receptor sites. (Kaliner Tr. 474:17-475:5). The POOS would have understood that the meaning of the term anti-allergic depends on the context in which it is used. (Kaliner Tr. 474:17-475:5).

D. Mast Cell Heterogeneity

1. Mast Cell Heterogeneity Was Well Known and Accepted by 1995

59. A major difficulty skilled artisans had in finding a compound that was an effective human conjunctival mast cell stabilizer was the recognition by the mid-1980s of "mast cell heterogeneity." (Yanni Tr. 132:13-133:14; Kaliner Tr. 484:4-485:3). Mast cell heterogeneity means that mast cells in different species, and in different tissues within the same species, are different from one another and have different biological responses to, for instance, stimuli and attempts to stabilize them. (Yanni Tr. 132:19-22; Kaliner Tr. 475:6-480:10).

60. As far back as the 1970s, researchers in the area knew that mast cells were different and responded to stimuli and attempts to stabilize them differently. (Kaliner Tr. 475:9-476:2).

61. Mast cell heterogeneity was well known to the POOS by 1995, and numerous scientific publications confirming it had been published by that time. (Yanni Tr. 140:7-11; Kaliner Tr. 476:3-24, 480:16-483:11; TX 103A; TX 69A; TX 221A; TX 219; Bielory Tr. 1136:8-1137:1; Abelson Tr. 1732:18-25). Apotex is not challenging that mast cell heterogeneity was well-known by 1995. Its expert

agrees with Alcon's experts, Dr. Mark Abelson ("Dr. Abelson") and Dr. Michael Kaliner ("Dr. Kaliner"), that by 1995, the POOS understood that "[t]he concept of mast cell heterogeneity has emerged as a fundamental principle for the understanding of the possible roles of the mast cells in health and disease." (Bielory Tr. 1137:10-22; Kaliner Tr. 481:25-482:8; Abelson Tr. 1732:20-1733:14; TX 69A).

62. The specification of the '805 patent discusses and describes mast cell heterogeneity and also refers to various prior art references discussing this concept. (TX 3A; Yanni Tr. 142:9-146:12).

2. MCT and MCTC Mast Cells in the Human Body

63. In the early 1990s, it was widely accepted that there were at least two types of mast cells within the human body. (Yanni Tr. 134:19-23; Kaliner Tr. 480:11-482:19; TX 69A; TX 103A). Based on a protease contained in their granules, these mast cells were referred to as MCT, or tryptase containing mast cells, and MCTC, or tryptase and chymase containing mast cells. (Yanni Tr. 134:19-135:5; Kaliner Tr. 476:3-24; Bielory Tr. 1051:25-1052:21; TX 69A; TX 103A).

64. The mast cells in the eye and skin are both primarily MCTC mast cells. (Yanni Tr. 135:6-13; Bielory Tr. 1051:25-1052:21; 1140:5-1141:8; TX 69A at 147; TX 103A at 35). The mast cells in the nose and the lung are primarily MCT. (Yanni Tr. 135:14-18; TX 69A at 147; TX 103A at 35).

65. Animal mast cells are not classified using the MCT or MCTC classifications.

(Yanni Tr. 135:19-23; TX 69A; TX 103A).

66. In their 1989 article, Dr. Irani and Dr. Schwartz published data showing the relative populations of MCT and MCTC mast cells in various tissues in the human body. (Yanni Tr. 137:13-23; TX 69A). The following year, Dr. Irani and Dr. Butrus published data showing the relative populations of MCTC and MCT mast cells in the eye during both normal and diseased states. (Yanni Tr. 137:13-138:2; Kaliner Tr. 480:11-481:12; TX 103A at 37-39). The data shows that the mast cells in the human eye are predominantly MCTC mast cells regardless of whether there is an allergic condition. (Yanni Tr. 137:24-138:2; Kaliner Tr. 480:11-481:12; TX 103A at 37-39).

67. In the early 1990s, workers in the field of allergic eye disease did not know if mast cells in the human skin were different from mast cells in the human eye, or whether the response of mast cells in the skin would be indicative of the response of mast cells in the eye because both were known to be primarily MCTC mast cells. (Yanni Tr. 138:15-23; TX 69A; TX 103A).

68. By 1995, it was known that with regard to mast cell populations, the closest tissue to the human conjunctiva was the human skin. (Yanni Tr. 138:11-14; Kaliner Tr. 481:8-12; TX 69A at 147; TX 103A at 35). It was also known that with regard to mast cell populations, the closest tissue to the human conjunctiva was the human skin. (Yanni Tr. 138:11-14; Kaliner Tr. 481:8-12; TX 69A at 147; TX 103A at 35).

69. In 1996, Dr. John Yanni ("Dr. Yanni") of Alcon published the first data comparing mast cells in the skin and the eye that shows that mast cells in the skin and the eye are very similar, but not identical, to one another. (Yanni Tr. 140:12-23).

3. Because of Mast Cell Heterogeneity, Testing on Animal Mast Cells Is Not Applicable to Human Mast Cells

70. Because mast cells are different and respond to attempts to stabilize them differently, a researcher cannot extrapolate results from animal mast cell studies to human mast cells or tests from one tissue in the human body to another tissue within the human body. (Yanni Tr. 132:23-133:14; Kaliner Tr. 477:10-478:11). Therefore, those searching for a human conjunctival mast cell stabilizer could not use animal data to obtain an expectation about what would happen in humans, nor could they use data from different human tissue testing. (Yanni Tr. 133:6-14; Kaliner Tr. 477:10-478:11, 484:4-485:3; Abelson Tr. 1733:1-14).

71. By 1995, this concept was understood by the POOS, who would not have expected that a compound which appeared to be a mast cell stabilizer in animal tests would be a mast cell stabilizer in humans. (Kaliner Tr. 484:4-485:3, 477:10-21). The compound would have to be tested in the target human tissue mast cells to determine if it could stabilize those specific mast cells. (Abelson Tr. 1733:8-14; Kaliner Tr. 484:4-14). In 1995, Dr. Yanni also did not expect that a compound that appeared to be a mast cell stabilizer in animal tests would also be a mast cell stabilizer in humans. (Yanni Tr. 153:3-153:7). Dr. Yanni believed that the

compound of interest would have to be tested in the target human tissue mast cells to determine if it could stabilize those specific mast cells. (Yanni Tr. 153:3-153:7).

72. Because of mast cell heterogeneity, the POOS would not conclude that mast cell stabilization in other tissue mast cells within a human would mean that the compound would stabilize human conjunctival mast cells. (Kaliner Tr. 540:22-541:6).

4. Mast Cell Heterogeneity Does Not Mean that All Animal Testing Is Useless for All Purposes

73. There are animal tests that are predictive for certain types of activity not involving stabilizing mast cells. For instance, guinea pig models are useful for testing a compound's antihistaminic activity, or evaluating the topical ocular availability of a compound. (Yanni Tr. 133:18-134:2, 151:12-23). Animals are useful for screening, and researchers understand that they have to test in animals first. (Kaliner Tr. 485:4-20). But for testing mast cell stabilization, mast cell heterogeneity requires species and tissue specificity in order to have an expectation regarding a compound's ability to stabilize mast cells in the human eye. (Yanni Tr. 133:18-134:2; Kaliner Tr. 484:4-485:3; Abelson Tr. 1733:1-14).

E. The Biphasic Effect of Antihistamines

1. The Biphasic Effect Was Well Known by the 1990s

74. For several decades prior to 1995, researchers in the field knew that antihistamines

have the ability to prevent mediator release from mast cells at low concentrations, but that they actually cause the release of mediators at slightly higher concentrations. (Yanni Tr. 154:12-18; Kaliner Tr. 511:6-514:6; TX 709; TX 735).

75. By 1995, this "biphasic effect" was well known in the art, had been repeatedly described in publications, and was known to be a common feature of antihistamines. (Yanni Tr. 154:1-14; Kaliner Tr. 514:7-11; Bielory Tr. 1235:20-1236:12; TX 709; TX 735; TX 738A; TX 741). There are published discussions of the biphasic effect from 1952 through the 1990s. (Yanni Tr. 154:15-18; Kaliner Tr. 511:6-514:6; Bielory Tr. 1235:20-1236:12; TX 709; TX 735; TX 738A; TX 741).

2. The Biphasic Effect Is Caused by Non-Specific Action on Cell Membranes

76. The biphasic effect of antihistamines affects all cells, not just mast cells, because it is caused by an interaction between the compound and the cell membrane. (Yanni Tr. 154:1-11; Kaliner Tr. 509:24-511:5, 755:3-6, TX 735; TX 227; AA-21.01-.08).

77. At low concentrations, antihistamines infiltrate the membranes of cells and cause them to become rigid, which prevents mediators from being secreted through the membrane. (Yanni Tr. 156:18-23; Kaliner Tr. 514:12-516:21; TX 735; TX 227; TX 21.01-.08). However, at slightly higher concentrations, the increased infiltration of the cell membrane causes increased intracellular surface pressure that damages the cell membrane, releasing all pre-formed mediators. (Yanni Tr.

157:2-14; Kaliner Tr. 514:12-516:21; Bielory Tr. 1247:25-1248:6; TX 735; TX 227; AA-21.01-.08).

78. The biphasic effect of antihistamines is reproducible in every laboratory model that has been used to study it. (Kaliner Tr. 516:22-517:1).

79. While there have been no clinical studies designed to test the phenomenon, there is evidence that the release of mediators caused by higher concentrations of antihistamines does occur *in vivo*[2] in the human eye, including punctuate keratitis that occurred with the .05% concentration of ketotifen, a potent antihistamine. (Yanni Tr. 161:11-162:12; Kaliner Tr. 518:11-519:3; Bielory Tr. 1242:21-25). Other clinical evidence consistent with the biphasic effect occurring *in vivo* includes the stinging caused by antihistamine eye drops and the large amounts of swelling and edema caused by local injection of antihistamines. (Kaliner Tr. 519:4-25).

3. Measuring Effect on Mast Cells Using the Human Conjunctival Mast Cell Assay

80. The human conjunctival mast cell ("HCMC") assay is an *in vitro* model for assessing a test compound's effect on the release of histamine from a mast cell at different concentrations. (Yanni Tr. 162:21-165:18). The HCMC model was designed by Dr. Yanni and Steve Miller ("Mr. Miller"), both of Alcon. (Yanni Tr.

[2] "*In vivo*" tests are done in a live animal. By contrast, "*in vitro*" tests are usually conducted directly on cells removed from an animal or human.

162:21-165:18; Miller Tr. 1502:8-13). The test involves a series of controls to validate the accuracy of the test. (Yanni Tr. 165:19-167:15).

81. The results of the HCMC test are typically graphed on a logarithmic scale, meaning that the left side of the X-axis reflects very small differences in concentration, while the right side of the X-axis reflects larger differences in concentration. (Yanni Tr. 172:8-16; Kaliner Tr. 522:14-523:2, 527:19-528:3). Scientists graph data using a logarithmic scale, which allows a wide range of concentrations of a compound to be plotted on the same graph. Each increment on a log scale is a ten-fold increase in concentration. (Kaliner Tr. 527:19-528:3).

82. The Y-axis of the chart shows the percentage of inhibition of histamine release. (Yanni Tr. 165:9-15, 170:7-21).

83. Zero on the Y-axis reflects that no histamine release has been inhibited. Below the zero line reflects that there has been stimulation or "potentiation" of histamine release. (Yanni Tr. 170:7-171:1; Miller Tr. 1512:23-1513:4). Compounds whose curves go up and then drop down are biphasic compounds. (Yanni Tr. 171:2-9).

4. The "Inhibitory" Effect of Biphasic Antihistamines at Low Concentrations Is Not Clinically Relevant Mast Cell Stabilization

a. The POOS Did Not Consider Biphasic Compounds To Be Mast Cell Stabilizers

84. In 1995, the POOS did not consider the inhibition of histamine release seen on the left side of the biphasic curves of antihistamines to represent biologically or

clinically relevant mast cell stabilization. (Kaliner Tr. 526:10-13, 535:10-535:14). Scientists who have observed the biphasic effect of antihistamines on histamine release have found that while antihistamines have been shown to have some stabilizing effect on mast cells, the effect is typically not at pharmacologically relevant doses. (Kaliner Tr. 532:15-21, 533:1-533:8; TX 724).

85. The biphasic curves generated by antihistamines do not reflect biological mast cell stabilization because they do not follow a typical dose response curve, which would have a plateau and not a sharp drop-off. (Kaliner Tr. 525:1-526:9; AA-23; AA-1.03).

86. The POOS in 1995 would have been aware of the biphasic effect of antihistamines, that it occurred as a result of a lipophilic compound penetrating the cell membrane, and that this phenomenon was not useful for stabilizing human conjunctival mast cells. (Kaliner Tr. 534:3-24).

b. It Is Impossible to Give Patients a Dose of a Biphasic Compound that Would Cause Mast Cell Stabilization and Not Mast Cell Degranulation

87. Precise dosing of ophthalmic drugs cannot be predicted with certainty as a result of variability of many factors that affect the absorption rate, including the patient's age, the patient's blinking habits, the patient's ability to administer the drop in the eye, the patient's eye health, and the amount of fluid on the patient's eye. (Banker Tr. 921:24-922:23, 923:22-924:5). For these reasons, most ophthalmic products are dosed much higher than is minimally effective. (Banker Tr. 942:18-943:5).

Given this variability, it is much easier to formulate an ophthalmic product when you have a wide range of effective concentrations as opposed to a narrow range of concentrations. (Banker Tr. 927:10-17).

88. It would not be possible to use a biphasic antihistamine as a clinically relevant mast cell stabilizer because it is not possible to achieve the concentration at which biphasic antihistamines prevent the release of mediators in the actual human eye. (Kaliner Tr. 527:3-532:14). This is because the concentration at which these concentrations appear to show inhibition is too low to get across the barrier of the conjunctival membrane, and the range of an effective dose is so small, that it would be impossible to dose reliably in that narrow range given the variability in the application of eye drops and the variability among different patients. (Kaliner Tr. 527:3-532:14; AA-33; AA-74).

89. Even Apotex's expert, Dr. Banker, agrees with that assessment. (Banker Tr. 943:11-15 (Q: Dr. Banker, if you were choosing a compound to act as a mast cell stabilizer in the human eye, from a formulation and dosing perspective, would it be preferable if the compound were not biphasic? A: I believe that would certainly be preferable.")).

90. While Apotex's other expert, Dr. Leonard Bielory ("Dr. Bielory"), opined that biphasic compounds could be mast cell stabilizers, he never addressed the fact that the concentration range at which biphasic compounds show an inhibitory effect is too narrow and too small to provide that dose to the mast cells in the human eye.

He also testified that while he disagreed with the position taken by Dr. Yanni that olopatadine is a superior mast cell stabilizer compared to biphasic compounds that reach their peak inhibition at lower concentrations, Dr. Yanni's position was "not an unreasonable" one. (Bielory Tr. 1248:20-1249:10).

91. Viewing the dose response curves of biphasic antihistamines on a non-logarithmic scale shows the linear relationship between the concentration used and the effect on mediator release. (Yanni Tr. 172:3-18).

92. Viewing the data in non-log format illustrates why biphasic antihistamines are not clinically relevant mast cell stabilizers. (Kaliner Tr. 527:18-528:13; AA-74). The range of effective concentrations is so narrow and so small, that the concentrations at which biphasic antihistamines appear to inhibit histamine release cannot be used to effectively stabilize human conjunctival mast cells. (Yanni Tr. 160:24-161:10; AA-74).

F. The Invention of Patanol®

1. Alcon's Screening of Compounds

93. When Dr. Yanni arrived at Alcon in 1990, he worked with Dr. Stella Robertson ("Dr. Robertson") and developed a strategy to try to find a treatment for seasonal or perennial allergic conjunctivitis, as that type of conjunctivitis accounts for 95% of all allergic conjunctivis cases. (Yanni Tr. 128:13-129:8). Their goal was to find a chemical molecule with an antihistamine component and also a mast cell stabilizing component. (Yanni Tr. 129:9-21). The advantage of such a dual-action

compound is that it could provide immediate relief to a patient undergoing an allergic reaction by blocking histamine through its antihistaminic effect and prevent further allergic symptoms through its mast cell stabilizing effect. (Yanni Tr. 129:9-21; Kaliner Tr. 554:22-555:10).

94. In order to find such a compound with both an antihistaminic and mast cell stabilizing component, Alcon obtained compounds that had been described as anti-allergic in order to test them in Alcon's allergy models. (Yanni Tr. 151:12-152:16, 201:23-202:3).

95. Most of the compounds Alcon tested had previously-generated data from other pharmaceutical companies showing that they had a general anti-allergic effect. (Yanni Tr. 202:4-16). The standard assay used was an *in vivo* model of anaphylaxis known as the rat Passive Cutaneous Anaphylaxis ("PCA") model. (Yanni Tr. 202:7-10). This model tests the "local allergic activity in the skin that [is] typically measured by swelling or a release of a dye from the vasculature of the animal." (Yanni Tr. 203:1-4).

96. The fact that a compound had activity in a rat PCA test, or another test demonstrating that the compound had anti-allergic properties, did not mean, however, that the compound would be a mast cell stabilizer. (Yanni Tr. 202:17-203:17). Inhibition in these models meant that there had been a general inhibition of the allergic reaction, and did not establish that mast cell stabilization had occurred or that the compound would be active in the HCMC assay. (Yanni Tr.

203:18-204:15, 204:23-205:2).

97. At the time Alcon was doing its testing, other pharmaceutical companies also were searching for mast cell stabilizers to treat allergies in the human body, including the eye. (Yanni Tr. 130:8-132:5).

98. The concept of mast cell heterogeneity meant that the POOS would not have a reasonable expectation that a compound would be a mast cell stabilizer in the human conjunctiva based on animal tests. (Kaliner Tr. 484:4-485:3, 477:24-478:14). However, in 1990, there was no human conjunctival mast cell test available, and Dr. Yanni and others at Alcon therefore decided to develop a HCMC assay. (Yanni Tr. 133:15-17, 162:21-165:15).

99. The HCMC model is a scientifically valid model and was a huge step forward in allowing scientists to investigate the effect of various agents on human conjunctival mast cells. (Kaliner Tr. 524:2-7).

2. Alcon's Determination that Olopatadine Could Be Used to Stabilize Human Conjunctival Mast Cells

100. Alcon obtained a test compound named olopatadine (the Z isomer) from Kyowa under a License and Supply Agreement dated July 27, 1993. (Yanni Tr. 205:3-19; 286:11-16; TX 24).

101. When Dr. Yanni first received olopatadine, he was advised that it was a non-steroidal anti-inflammatory agent. (Yanni Tr. 205:3-19; *see also* Robertson Dep. 19:8-12 (testifying that Alcon originally tested olopatadine as an anti-

inflammatory agent). Olopatadine was not active in the assays used to test non-steroidal anti-inflammatory drugs. (Yanni Tr. 205:20-206:1).

102. Alcon then learned that there must have been a misunderstanding as it was informed by Kyowa that olopatadine was an anti-allergy drug. (Yanni Tr. 206:2-8; Yanni Dep. 18:24-19:21).

103. Before testing olopatadine, Dr. Yanni understood that olopatadine was an antihistamine, and was concerned that olopatadine would be biphasic. (Yanni Tr. 206:17-22). Alcon therefore needed to test olopatadine to the limits of its solubility, because Alcon was not interested in developing biphasic compounds as mast cell stabilizers. (Yanni Tr. 207:25-209:11).

104. Upon testing olopatadine in the HCMC assay, *see* TX 971, Alcon learned that olopatadine inhibits the release of histamine from human conjunctival mast cells at all concentrations tested up to its limit of solubility – in other words, that olopatadine stabilizes human conjunctival mast cells to an extent that would be clinically relevant. (Yanni Tr. 208:2-209:11).

105. Alcon's testing demonstrated that olopatadine was topically bioavailable, that it was a moderately potent antihistamine with a long duration of action, and that it was a human conjunctival mast cell stabilizer. Alcon therefore decided to develop olopatadine, which ultimately resulted in the approval and introduction to the market of Patanol®. (Yanni Tr. 206:23-207:24).

106. Of all of the compounds that Alcon tested that had anti-allergy activity in animal

testing, only olopatadine turned out to be a human conjunctival mast cell stabilizer. (Yanni Tr. 204:16-22).

107. In clinical studies, Patanol® has proven to be a clinically effective mast cell stabilizer that inhibits all signs and symptoms of the allergic response, including signs and symptoms that are not usually attenuated or blocked with antihistamines. (Yanni Tr. 213:6-11).

III. Prosecution History

A. The '227 Application

108. On October 8, 1993, Mr. Patrick Ryan ("Mr. Ryan"), on behalf of Alcon and Kyowa, filed United States Patent Application # 08/134,227 ("the '227 application") with the United States Patent and Trademark Office ("PTO"). It was entitled "Topical Ophthalmic Formulations for Treating Allergic Eye Diseases." (TX 449 at ALP001-003004). The '227 application claimed the use of an olopatadine eye drop for use in the treatment of allergic eye disease. (TX 449 at ALP001-003014-15; Ryan Tr. 1559:17-25; Smith Tr. 1308:3-24, 1309:21-1310:4). The named inventors of the '227 application are the same as those of the '805 patent, namely, Dr. Yanni, Dr. Robertson, Eiji Hayakawa, and Masashi Nakakura. (TX 449 at ALP001-003017-18).

109. The specification of the '227 application also included a description of the concept of mast cell heterogenity. (TX 449 at ALP001-003005-6; Ryan Tr. 1561:20-1563:21). As part of that discussion, the specification included Table 1 to show

that well-known compounds reported in the literature as mast cell stabilizers in animals or other tissues – namely cromolyn and nedrocromil[3] – were not effective mast cell stabilizers when tested on the specific mast cells in the human conjunctiva. (TX 449 at ALP001-003009-11; Ryan Tr. 1563:22-1564:13; Yanni Tr. 220:20-221:3).

110. On December 30, 1993, the patent examiner rejected each of the four pending claims as obvious in light of the United States Patent # 4,871,865 and United States Patent # 4,923,892 (the "Lever patents"). (TX 449 at APL001-003032). The examiner invited the applicants to submit data demonstrating unexpected properties over the prior art. (TX 449 at ALP001-003033; Ryan Tr. 1568:2-10; Smith Tr. 1310:8-1311:13).

B. Comparative Testing of Olopatadine (the Z and E isomer) and the Wellcome Compounds

111. In response to the examiner's rejection, individuals at Alcon under Dr. Yanni's direction conducted some experiments in order to determine whether there were unexpected results that could be shown. (Smith Tr. 1314:1014).

112. In February 1994, Alcon received samples of the Wellcome Compounds from Kyowa in limited quantities. (TX 425; Yanni Tr. 227:12-228:3).

113. Alcon thereafter performed three comparative tests of olopatadine (the Z and E

[3] Cromolyn and nedrocromil are not within the Lever patents and were never cited as prior art to the '227 application or the '805 patent.

isomers) and the Wellcome Compounds, and reported the results in a report to Kyowa known as the Kyowa Report. (TX 100; TX 244; TX 995; TX 1151; Ryan Tr. 1567:14-20).

114. Table 1 of the Kyowa Report contains the results of Alcon's comparative anti-allergic testing of olopatadine and the Wellcome Compounds in a passive anaphylaxis in rat conjunctiva ("PARC") test. (TX 100 at ALP001-002286; Yanni Tr. 279:21-281:17-24). Figure 1 of the Kyowa Report contains the results of an *in vitro* test comparing the mast cell stabilizing effects of olopatadine and the Wellcome Compounds on human conjunctival mast cells ("Wellcome HCMC test"). (TX 100 at ALP001-002287; Bielory Tr. 1117:18-1121:1; Yanni Tr. 280:21-281:1). Figure 2 of the Kyowa Report contains the results of Alcon's *in vitro* test comparing the mast cell stabilizing effects of the Z- and E-isomers of olopatadine on human conjunctival mast cells ("Z-E HCMC test"). (TX 100 at ALP001-002287; Yanni Tr. 281:8-11).

115. Dr. Yanni believed the results of the testing were very favorable to olopatadine as compared to the Wellcome Compounds. The PARC tests showed that both olopatadine and the E isomer were significantly more active than Wellcome I and Wellcome II. (Yanni Tr. 279:21-280:20). Although the Wellcome HCMC tests were inconclusive as to Wellcome Compounds I and II, the upward slope on the left sides of their curves, coupled with the "rapid" downward slope in the second half of their curves, was consistent with those of biphasic compounds. (Yanni Tr.

246:9-249:9, 268:18-269:10; *see also* TX 244).

116. Trial Exhibit 419 contains the compound status reports for Wellcome Compounds I and II dated March 23, 1994. For both compounds, Dr. Yanni checked the box that said "no further interest" because he was not interested in further developing the Wellcome Compounds. (TX 419 at ALP-013-113813-14). Dr. Yanni testified that he had "no further interest" in the Wellcome Compounds because the test data Alcon had generated showed that olopatadine had superior activity in the PARC test and suggested that Wellcome I and II were biphasic. (TX 419; Yanni Tr. 269:11-272:8).

117. Dr. Yanni also checked the box that said "no further interest" for the E isomer of olopatadine because he was not interested in developing the E isomer. (TX 419 at ALP-013-113812). Dr. Yanni had data that the E isomer was equivalent to olopatadine, but not superior to olopatadine, so there was no advantage to the E isomer over the compound he already had. Moreover, because of Kyowa's work with the compound, there was already a body of olopatadine test data in existence that Alcon could rely on addressing such issues as toxicology, genotoxicity, and carcinogenicity; whereas with the E isomer, all of the data would have to be generated, which would have delayed development of any E-isomer-based product. (TX 419 at ALP-013-113812; Yanni Tr. 275:6-276:19).

118. Even though Dr. Yanni was not interested in developing the E-isomer, he was still interested in getting a license to it, as he was concerned about a competitor

developing it. (TX 419; Yanni Tr. 275:6-176:19).

C. The Continuation-In-Part Application and the Abandonment of the '227 Application

119. Unlike the comparison between olopatadine and Wellcome I and II, there was no significant difference between olopatadine and its E isomer. (TX 442). As a result, Mr. Ryan believed that he had a problem because the E isomer was the closest prior art to the '227 application claims, but he could not show superiority over it. (Ryan Tr. 1587:9-22). He did not believe that he could disclose only the favorable data showing that olopatadine was superior to Wellcome I and II, but withhold the E isomer data that showed that the E isomer was as good as olopatadine. (Ryan Tr. 1587:9-22, 1587:23-1588:15).

120. Given his understanding of the test results, Mr. Ryan decided to prepare a continuation in part ("CIP") application that would claim the use of both olopatadine and the E isomer. With these new claims, the closest prior art would become the Wellcome I and II Compounds, and he could use the data that he understood existed to assert unexpected properties of olopatadine and the E isomer over those compounds, as he understood that olopatadine and the E isomer were superior to Wellcome I and II. (Ryan Tr. 1569:11-1571:8, 1572:2-22; Smith Tr. 1397:7-19).

121. In the spring of 1994, Mr. Ryan prepared a draft CIP application, which took the original '227 application and added the E isomer to the description and the claims.

(Ryan Tr. 1570:6-1571:3, 1572:2-24; TX 2069).

122. In addition, Mr. Ryan added Table 2, which compares the Z and E isomers at a dose of 500 uM, to show that olopatadine and the E isomer behaved similarly in the Z-E HCMC test. (TX 2069; Ryan Tr. 1598:15-25).

123. Mr. Ryan also added the Kyowa Report's description of the PARC test data and the data from Table 1 (the PARC test data) in preparing Table 3. (*Compare* TX 2069 at ALP001-002355-56, *with* TX 794 at ALP001-002285-86).

124. Mr. Ryan did not add the Wellcome HCTMC test data that is reflected in Figure 1 of the Kyowa Report.

125. Around this time frame, Kyowa, Alcon's licensing partner, wrote a letter to Alcon, stating that Kyowa "would not like to disclose any biological data for the E-isomer to [sic] outside of Kyowa and Alcon" because of Japanese regulatory issues. The letter further states that "[i]n this regard, we would cordially ask that the data of E-isomer should not be included in our joint patent application for ophthalmic use." (TX 774; Ryan Tr. 1574:25-1575:14).

126. Mr. Ryan believed that it would be improper to submit data to the PTO showing that olopatadine was superior to Wellcome Compounds I and II, but withhold data showing that olopatadine was not superior to the closest prior art compound, the E isomer. Because he could not submit the E isomer data, and did not believe that it would have been proper to go forward without it, Mr. Ryan abandoned the '227 application in July 1994 and did not file the CIP. (Ryan Tr. 1575:15-1576:21; TX

449 at ALP001-003042-43; Smith Tr. 1322:3-7).

D. The ‘729 Application

127. Kyowa subsequently allowed the disclosure of the E isomer data, and on June 6, 1995, the ‘729 application, which led to the ‘805 patent, was filed by Alcon Laboratories, Inc. (Ryan Tr. 1595:12-1596:17; TX 4 ALP001-42001).

128. To prepare the ‘729 application, Mr. Ryan took the CIP application that he had prepared in 1994 and reformatted it so that it was an original application. The substantive work on the application had been done in 1994, and Mr. Ryan did not go back and review his file for the abandoned ‘227 application in preparing the ‘729 application. (Ryan Tr. 1595:12-1596:17; TX 2070; TX 2071).

129. Like the CIP, the ‘729 application claimed methods of treating allergic eye disease using both (or either) olopatadine and the E isomer, including the data about the E isomer that Mr. Ryan had wanted to disclose to the PTO. (TX 4 at ALP001-042004-5, ALP001-042008, ALP001-042022-23; Ryan Tr. 1559:17-1560:3. 1597:7-19; Smith Tr. 1324:23-1325:13; TX 449; TX 2069).

130. The application was assigned to a different examiner than the previous ‘227 application. (TX 4 at ALP001-042001; Smith Tr. 1324:7-10).

131. The specification of the ‘729 application included the same Table 1 as had been included in the ‘227 application for the same purpose: demonstrating the principle of mast cell heterogeneity. (Ryan Tr. 1598:1-14; Yanni Tr. 311:18-312:23).

132. The specification also contained Tables 2 (comparison of the Z and E isomer) and

3 (PARC test comparing olopatadine to the Wellcome Compounds), which had been added to the draft CIP application. (TX 4; TX 2069).

133. The results of the Wellcome HCMC test, which compared the mast cell stabilizing effects of olopatadine and the Wellcome Compounds on human conjunctival mast cells, and is reflected in Figure 1 of the Kyowa Report, was not included in the '729 application. (*See* TX 4).

134. Contemporaneous with the filing of the '729 application, Alcon and Kyowa filed an Information Disclosure Statement disclosing to the PTO the Lever patents, the '863 patent, the Hamilton paper, and seven additional references, including all of the references that were identified during the prosecution of the '227 application. (TX 4 at ALP001-042028-29).

E. The Rejection and Amendment

135. On July 17, 1996, the examiner issued an office action rejecting claims 1-12 of the '729 application. (TX 4 at ALP001-042082-88). The examiner rejected claims 1-8 as anticipated under 35 U.S.C. § 102 by Kamei, and rejected claims 1-12 as obvious under 35 U.S.C. § 103 over Kamei as applied to claims 1-8, and also over Kamei in combination with the Lever '892 patent. (TX 4 at ALP001-042085; Ryan Tr. 1607:8-1608:4; Smith Tr. 1334:16-20).

136. In response to the office action, Mr. Ryan submitted an amendment to the PTO on October 7, 1996. (TX 4 at ALP001-042089-94). Mr. Ryan amended claim 1 to recite that the claimed method is for treating allergic eye diseases "in humans" and

to require that the method comprise "stabilizing conjunctival mast cells." (TX 4 at ALP001-042089; Ryan Tr. 1609:1-8; Kilworth Tr. 1988:17-1989:6). He then presented argument to the PTO. (TX 4 at ALP001-042092-94; Ryan Tr. 1609:9-12).

137. In response to the examiner's obviousness objection based on Kamei and the Lever '892 patent, Mr. Ryan made four alternative arguments in numbered paragraphs (i) through (iv). (TX 4 at ALP001-042092-94). His argument in paragraph (iv) is discussed *infra*. In numbered paragraph (ii), Mr. Ryan discussed mast cell heterogeneity, arguing that "as the data in Applicant's Specification illustrates, not all compounds which are known to be mast cell stabilizers in rats are effective human conjunctival mast cell stabilizers." (TX 4 at ALP001-042093; *see also* Kaliner Tr. 674:10-23).

138. In paragraph (iv), Mr. Ryan argued that even if one ignored his prior arguments, there is "no way to predict, given the disclosures of Kamei et al. and Lever, that the compounds recited in Applicants' Claims would possess significantly superior conjunctival mast cell stabilization activity compared to the structurally similar compounds exemplified by Lever." (TX 4 at ALP001-042094). He then referred to Table 3 of the specification (the PARC test data) and explained that it "illustrates the statistically significant superior mast cell stabilization activity that the Z- and E- isomers of the 2-acetic acid derivative [olopatadine and the E isomer] have compared to the 2-carboxylic acid and 2-acrylic acid derivatives

exemplified by Lever [Wellcome I and II]." (TX 4 at ALP001-042094).

139. As noted above, on June 24, 1997, the '805 patent issued. (Docket # 173, Stipulation ¶ 7).

IV. '805 Patent

140. Claim 1 of the '805 patent reads:

> A method for treating allergic diseases in humans comprising stabilizing conjunctival mast cells by topically administering to the eye a composition comprising a therapeutically effective amount of 11-(3-dimethylaminopropylidene)-6, 11 -dihydrodibenz[b,e]oxepin-2-acetic acid or a pharmaceutically acceptable salt thereof.

(TX 3A, col. 7, ll. 28-34).

141. Olopatadine is a particular three-dimensional form of 11-(3-dimethylaminopropylidene)-6, 11-dihydrodibenz[b,e]oxepin-2-acetic acid, and is referred to as the "cis" or "Z" isomer of the compound. An alternative isomer having the same atoms bonded in the same sequence but differing in their orientation in three-dimensional space is called the "trans" or "E" isomer. (Docket # 173, Stipulation ¶ 11).

142. Olopatadine is also sometimes referred to as KW-4679 or AL4943A. (Docket # 173, Stipulation ¶ 12).

143. In the '805 patent, the use of the term 11-(3-dimethylaminopropylidene)-6, 11-dihydrodibenz[b,e]oxepin-2-acetic acid refers to olopatadine, its E isomer, or mixtures of both. (TX 3A, col. 7, ll. 28-34).

144. Claims 2 through 8 of the ‘805 patent are dependent claims stemming from claim 1, each adding various limitations. (TX 3A, col. 7, l. 35 – col. 8, 1. 22).

145. Dependent claims 2, 3, and 4 limit the method of claim 1 to methods using solutions in which the amount of olopatadine in the composition is limited to about 0.0001 to 5% w/v, about 0.001 to about 0.2% w/v, and about 0.1% w/v, respectively. (TX 3A at col. 7, l. 35 – col. 8, l. 3).

146. Dependent claim 5 is limited to methods using compositions employing the “Z isomer” “substantially free” of the “E isomer.” (TX 3A, col. 8, ll. 4-11). The ‘805 patent defines “substantially free” as meaning that there is “less than about two percent” of the other isomer present in conjunction with the desired isomer. (TX 3A, col. 3, ll. 15-17).

147. Dependent claims 6, 7, and 8 are further limited to methods using compositions in which the Z isomer is limited to about 0.0001 to about 5% w/v, about 0.001 to about 0.2% w/v, and 0.1% w/v, respectively. (TX 3A, col. 8, ll. 16-22).

V. Infringement

148. Plaintiffs allege that Apotex’s filing of ANDA # 78-350 is an act of infringement of claims 1-8 of the ‘805 patent under 35 U.S.C. § 271(e)(2)(A). Plaintiffs further allege that Apotex is liable for inducing infringement under 35 U.S.C. § 271(b) and for contributory infringement under 35 U.S.C. § 271(c).

A. Apotex’s ANDA Product Infringes Claim 1 of the ‘805 Patent

149. Claim 1 of the ‘805 patent, as construed by the court, requires that Apotex’s

ANDA product stabilizes mast cells to a clinically relevant extent in the human eye. (*See* Docket # 282). The only issue in dispute is whether Apotex's ANDA product meets this limitation.

150. Dr. Michael Kaliner ("Dr. Kaliner"), Alcon's expert witness in allergies and a practicing physician, testified that, in his opinion, Patanol® is a clinically effective mast cell stabilizer in the human eye. (Kaliner Tr. 543:4-10). Patanol® blocks mast cell degranulation not only because it blocks itching, a common symptom associated with histamine, but also because it blocks symptoms that antihistamines alone cannot resolve, including swelling, irritation, tearing, and redness. (Kaliner Tr. 543:8-10; *see also* Yanni Tr. 210:15-19, 213:6-15 (Patanol® is clinically effective as a mast cell stabilizer in humans because of "the clinical utility noted with the compound . . . , being able to inhibit all signs and symptoms of allergic response, including signs and symptoms that are not typically effective or particularly attenuated or blocked with antihistamines.").

151. Dr. Kaliner also testified that, based upon his review of the relevant peer-reviewed scientific literature, Apotex's ANDA product would likewise stabilize conjunctival mast cells to a clinically relevant extent in the human eye. (Kaliner Tr. 563:11-19 ("[A] huge body of information published in the peer-reviewed literature . . . demonstrates that [Patanol®] inhibits mast cell degranulation, and does so in a clinically effective way in humans in the eye.").

152. Apotex's ANDA product is "the same product as Patanol®." (Kaliner Tr. 561:15-

18). Apotex's ANDA product contains "the same active and inactive ingredients in the same concentration" as in Patanol®. (Kaliner Tr. 561:2-18; TX 131 at ANDA000011). In its ANDA, Apotex represented to the FDA that "[t]he drug product described herein is equivalent to PATANOL® (Olopatadine Hydrochloride Ophthalmic Solution), 0.1%, marketed by Alcon Laboratories, Inc." (TX 131 at ANDA000038; *see also* TX 131 at ANDA000008 (the "conditions of use, active ingredient, inactive ingredients, dosage form, route of administration and strength of [Apotex's ANDA product]" are the same as Patanol®)).

153. Because Apotex's product "[c]ontains the same active and inactive ingredients in the same concentration as" Patanol®, Apotex requested a waiver of evidence showing *in vivo* bioequivalence. (TX 131 at ANDA000011).

154. Apotex's ANDA product will be used for the same use as Patanol® and administered the same way as Patanol®. (Kaliner Tr. 574:1-8, 578:1-8, 579:14-20). Apotex's ANDA product states that its product "will be administered . . . for the same indications as the 'listed' drug PATANOL®." (TX 131 at ANDA000009). The "Indications and Usage" sections of the labels for both Patanol® and Apotex's ANDA product are identical, listing only "the treatment of the signs and symptoms of allergic conjunctivitis." (TX 131 at ANDA 000029). Apotex's product "will be administered at the same dosage level, for the same duration and for the same indications" as Patanol®. (TX 131 at ANDA 000009; TX 131 at ANDA000030 (showing identical "Dosage and Administration"

sections for both Patanol® and Apotex's ANDA product labels)).

155. Like Patanol®, Apotex's ANDA product will stabilize human conjunctival mast cells to a clinically relevant extent. (Kaliner Tr. 563:11-24. *See also* TX 131 at ANDA 000017 (Apotex characterizes its ANDA product as an "inhibitor of histamine release from the mast cell," i.e., a mast cell stabilizer); Kaliner Tr. 561:19-562:5 (person of ordinary skill would understand this statement to mean that Apotex's product "will inhibit mast cell degranulation. It is a stabilizer of mast cells.").

B. Apotex's ANDA Product Infringes Claims 2-8 of the '805 Patent

156. In addition to meeting all of the elements of claim 1, use of Apotex's ANDA product also meets every limitation of dependent claims 2 through 8 of the '805 patent. These claims are discussed in Findings of Fact ## 144-47.

157. Apotex stipulated at trial that its ANDA product is a solution containing 0.1% w/v olopatadine and that its ANDA product contains 0.1% olopatadine, the Z isomer, substantially free of the E isomer. (Kaliner Tr. 572:16-19; *see also* TX 131 at ANDA000012 (ANDA product's proposed label states that "[e]ach mL contains: Olopatadine 1 mg."); TX 131 at ANDA000017 (stating that each mL of the ANDA product contains 1.11 mg of the hydrochloride salt form of olopatadine, which is "equivalent to 1 mg of olopatadine"); TX 131 at ANDA000017 (ANDA product contains "11-[(Z)-3-(Dimethylamino)propylidene]-6,11-dihydrodibenz[b,e] oxepin-2-acetic acid hydrochloride," which is the Z isomer – olopatadine

hydrochloride); TX 131 at ANDA00908, ANDA000912 (certificates of analysis of the olopatadine hydrochloride used in ANDA product showing the E-stereoisomer specification; specification is no more than 0.1%, which is below the 2% definition of substantially free; certificate of analysis shows no detectable E-stereoisomer found in ANDA product)).

VI. Validity of the '805 Patent

A. Obviousness

Apotex contends that claims 1-8 of the '805 patent are obvious under 35 U.S.C. § 103. The court will begin its discussion by defining the person of ordinary skill in the art.

1. Person of Ordinary Skill in the Art

158. Research teams in the area of allergic eye disease often are comprised of pharmacologists, immunologists, and medical doctors working in concert with each other. (Kaliner Tr. 457:5-19). The hypothetical POOS, as of June 6, 1995 (the '729 application's filing date), would have the relevant knowledge and skills of a pharmacologist, immunologist, and medical doctor. (Kaliner Tr. 457:5-19; Abelson Tr. 1746:4-7; *see also* Bielory Tr. 1056:16-1057:7).

159. The POOS would have years of postgraduate training and experience in developing and testing compositions or methods for treating allergic eye disease. (Kaliner Tr. 457:5-19; Abelson Tr. 8-12).

160. The POOS would know the literature, treatment, and the conventional wisdom of the field of allergic eye disease. The POOS would be familiar with *in vivo* and *in*

vitro models, and would understand the difference between testing in animals and humans. (Kaliner Tr. 457:21-458:4).

161. The POOS would understand the difference between mast cells in humans and mast cells in animals. (Kaliner Tr. 457:21-458:4; Abelson Tr. 1746:19-24).

162. The POOS would understand the allergy pathways, how they affect the eye, and the role of the mast cells within those pathways. The POOS would also understand the various methods for treating allergic eye disease, and the formulation of those various treatments. (Kaliner Tr. 458:5-14; Abelson Tr. 1746:13-18).

163. The POOS would focus on the data in those prior art references to understand what these references taught about the mechanism of action of the compounds being studied. (Kaliner Tr. 580:18-581:5; Abelson Tr. 1747:1-11). The POOS would assess the weight to be given to assertions in the prior art and would not rely upon speculative statements in patents or literature that were unsupported by data. (Kaliner Tr. 580:18-581:5 ("People can make claims and descriptions, but the data is where the information is, so that's what you need to look at."); Abelson Tr. 1747:1-1749:2 (testifying that a POOS would examine statements in a reference in light of the data).

2. The Scope and Content of the Prior Art

a. The Hamilton Article

164. In 1994, Hamilton *et al.* published an article entitled "Comparison of a New

Antihistaminic and Antiallergic Compound KW4679 with Terfenadine and Placebo on Skin and Nasal Provocation in Atopic Individuals" ("Hamilton"). (TX 159).

165. Hamilton was considered by the patent examiner who approved the '805 patent. (TX 4 at ALP001-042030).

166. Hamilton is significant because it represents the only testing of olopatadine in human tissues in the prior art. (Bielory Tr. 1167:14-17).

167. The article compares the effectiveness of orally administered terfenadine (an established and widely used antihistamine), placebo, and olopatadine in inhibiting allergic reactions in the skin and the nasal passages of human subjects. (TX 159).

168. Hamilton compared the effects of the test compounds on the skin in both a histamine challenge and an antigen challenge. (TX 159 at 956; Kaliner Tr. 596:3-24).

169. In the histamine challenge, histamine is injected into the skin to see how well the test compound inhibits the histamine-induced allergic reaction. (TX 159 at 956; Abelson Tr. 1761:16-1762:9). Histamine challenge does not involve the mast cells. (Kaliner Tr. 583:15-25). Olopatadine was effective in the histamine challenge in skin, indicating it worked as an antihistamine. (Abelson Tr. 1762:10-23).

170. In the antigen challenge, antigen is injected into the skin to see whether a compound inhibits the allergic reaction. (Kaliner Tr. 596:3-24). By itself, the

antigen challenge does not tell the POOS the mechanism of action of a compound, it just indicates whether a compound inhibited the allergic reaction. (Kaliner Tr. 596:25-597:8). However, when combined with a histamine challenge, the POOS gets insight into whether the antihistaminic action is the reason a compound is effective. (Kaliner Tr. 597:9-14).

171. Olopatadine was less effective in the antigen challenge in skin than in the histamine challenge, indicating that while it was effective as an antihistamine, it did not inhibit the release of other allergy-inducing mediators from the mast cells. (TX 159 at 959; Kaliner Tr. 597:25-598:5; Abelson Tr. 1763:1-16). The Hamilton Article authors thus concluded that olopatadine was not effective in keeping mediators in the mast cell – that is, it was not effective as a mast cell stabilizer. (TX 159 at 959; Kaliner Tr. 599:7-23; Bielory Tr. 1173:11-18; Abelson Tr. 1765:15-1766:3).

172. Apotex's expert, Dr. Bielory, agrees that Hamilton's data shows olopatadine to be a good antihistamine, but that there were mediators coming out of the mast cells upon antigen challenge that olopatadine did not inhibit or prevent from coming out of the mast cell. (Bielory Tr. 1173:11-16 ("Q: You're saying because it wasn't inhibiting the entire antigen-induced allergic reaction but it was a strong antihistamine, there had to be other mediators coming out of the mast cell, that [olopatadine] wasn't inhibiting or preventing from coming out of the mast cell? A: That is correct.")).

173. Hamilton thus taught the POOS that olopatadine was effective as an antihistamine but not effective as a mast cell stabilizer in the human skin. (Kaliner Tr. 599:4-13; Abelson Tr. 1760:18-1761:7, 1763:17-21, 1765:15-1766:3).

174. Human skin mast cells and human conjunctival mast cells are primarily classified as "MCTC." (Abelson Tr. 1764:5-23; Docket # 317, Alcon's Proposed Findings of Fact and Conclusions of Law, Ex. B). On a continuum of tissues, the POOS would consider the mast cells in the human skin to be the closest mast cells in any tissue or species to the mast cells in the human conjunctiva. (Abelson Tr. 1764:24-1765:12). The results in Hamilton's skin testing would thus teach the POOS that olopatadine was not an attractive candidate for a human conjunctival mast cell stabilizer. (Kaliner Tr. 599:14-23).

175. Hamilton was very close prior art, and it teaches away from the invention of claims 1-8 of the '805 patent by showing that olopatadine did not work as a mast cell stabilizer in its testing.

b. The Kamei Article

(1) Kamei Teaches Away from the Use of Olopatadine as a Mast Cell Stabilizer

176. In 1994, Kamei *et al.* published an article entitled "Effects of Certain Antiallergic Drugs on Experimental Conjunctivitis in Guinea Pigs" ("Kamei"). (TX 204).

177. Kamei describes the results of olopatadine (KW-4679) and four other compounds, chlorpheniramine, ketotifen, levocabastine, and amlexanox, in the eye of a guinea

pig. (TX 204).

178. Kamei was considered by the patent examiner who allowed the ‘805 patent. (TX 4 at ALP001-042088).

179. Kamei is significant because it is the only prior art reference that tested the effect of olopatadine in an eye. (Bielory Tr. 1150:4-7).

180. The Kamei authors compared the inhibition of the allergic reaction in the conjunctiva of a guinea pig in both an antigen-challenge model and a histamine-challenge model, and the data was compiled in Table 1. (TX 204 at ALP001-042345 (Table 1)). In the histamine challenge, the guinea pigs are dosed with histamine, and the allergic reaction is measured. (Kaliner Tr. 583:5-25). As in the Hamilton histamine challenge, a compound that is effective in this model can be characterized as an antihistamine, because it blocks the effect of the histamine that has been introduced into the subject’s system. (Abelson Tr. 1755:8-1756:23).

181. In this study, as in the Hamilton article, olopatadine showed stronger inhibition of histamine-induced conjunctivitis than of antigen-induced conjunctivitis. (Bielory Tr. 1150:18-25). From the data in Table 1, the Kamei authors concluded that olopatadine was effective as an antihistamine, but not effective as a mast cell stabilizer. (Kaliner Tr. 586:3-587:18; Abelson Tr. 1756:6-14; Bielory Tr. 1151:1-5).

182. Kamei also measured the release of histamine from mast cells into the conjunctiva. (TX 204 at 5; Abelson Tr. 1757:2-9). The results of this test show that olopatadine

was not effective in preventing histamine from being released by the mast cells; it was not a mast cell stabilizer. (TX 204 at ALP001-042345 ("[L]evocabastine . . . and amlexanox . . . significantly inhibited histamine release from the conjunctiva. The effects of . . . KW 4679 were not significant."); Abelson Tr. 1757:10-17).

183. Kamei also measured the release of histamine from mast cells into tears. (TX 204 at ALP001-042346; Abelson Tr. 1757:18-24; Kaliner Tr. 589:14-21). Figure 2 in Kamei reports the results, showing that olopatadine was not effective in inhibiting the release of histamine. (TX 204 at ALP001-042347; Kaliner Tr. 589:22-591:22; Bielory Tr. 1151:8-20). There is no statistical difference between olopatadine and the control, meaning olopatadine showed no inhibition of histamine release in this assay. (Kaliner Tr. 591:16-22; Bielory Tr. 1151:18-1152:8 (" . . . if data does not show a statistically significant difference, then a scientist cannot conclude that there's any difference at all . . .")). Again, this test confirmed that olopatadine was not effective as a mast cell stabilizer. (Abelson Tr. 1757:25-1758:15; Kaliner Tr. 589:14-21).

184. The Kamei authors concluded that olopatadine was not effective as a mast cell stabilizer. (Bielory Tr. 1149:18-1150:3; Kaliner Tr. 594:23-595:3). While olopatadine was shown not to have mast cell stabilizing properties, two other compounds, amlexanox and levocabastine, were shown to stabilize the mast cells. (Abelson Tr. 1755:6-1759:2; Kaliner Tr. 586:8-587:9 ("So the investigators themselves . . . interpreted the data to suggest that if you were looking for a mast

cell stabilizer at – based on these two experiments, you would look at levocabastine and amlexanox, and you would not look at chlorpheniramine, ketotifen, or KW4679.")).

185. The Kamei authors thus concluded that olopatadine was "not effective" in inhibiting release of histamine from mast cells. (TX 204 at ALP001-042347; Bielory Tr. 1149:18-1150:3). The POOS would be taught by Kamei that olopatadine did not act as a mast cell stabilizer. (Abelson Tr. 1758:16-1759:2).

186. Based on Kamei, the POOS would have concluded that amlexanox and levocabastine, and not olopatadine, acted as mast cell stabilizers in the guinea pig conjunctiva. (Kaliner Tr. 586:8-587:9). Based on Kamei, the POOS would have been motivated to pursue amlexanox and levocabastine, not olopatadine, as mast cell stabilizers. (Kaliner Tr. 594:23-595:14). Like Hamilton, Kamei teaches away from the claimed invention.

(2) Kamei Does Not Teach or Suggest the Use of Olopatadine at 0.1%

187. Kamei tested olopatadine as an eye drop in different protocols at all or some of the three concentrations, 0.0001%, 0.001%, 0.01% w/v. (TX 204 at ALP 001-042344; Bielory Tr. 1165:19-25). The 0.01% olopatadine eye drop specifically disclosed in the Kamei article falls within the range of concentrations in claims 1-3 and 5-7 of the '805 patent. (Kaliner Tr. 569:16-570:4; Banker Tr. 840:18-841:5, 1114:1-1115:8; Bielory Tr. 1165:15-1166:3).

188. These concentrations of olopatadine were substantially lower than 0.1% w/v (the w/v concentration of olopatadine in Patanol®). (Abelson Tr. 1759:14-21).

189. The POOS would not have had a reasonable expectation from Kamei that olopatadine would be effective at 0.1% w/v. (Abelson Tr. 1759:22-1760:14). At that dosage, the POOS would have been concerned that olopatadine (known at that time as simply an antihistamine) might be found to be biphasic. (Abelson Tr. 1759:22-1760:14). Thus, the POOS would not have been motivated by Kamei to use olopatadine at a concentration of 0.1%. (Abelson Tr. 1759:3-1760:14) (no expectation from Kamei as to effect of olopatadine at 0.1%); Kaliner Tr. 592:23-593:11).

c. The '863 Patent

190. The '863 patent, entitled "Dibenz[B,E]oxepin derivative and pharmaceutical compositions thereof," issued in 1992 and claims the olopatadine compound. (TX 6; Abelson Tr. 1766:15-17). The '863 patent discloses that olopatadine "is useful for the treatment of allergic conditions and inflammation." (TX 6, col. 3, ll. 4-5). Olopatadine is delineated as compound 20. (Docket # 173, Stipulation ¶ 16).

191. The '863 patent is owned by Kyowa. (TX 6).

192. The '863 patent was considered by the patent examiner who allowed the '805 patent. (TX 4 at ALP001-042030).

193. The '863 patent, as originally filed, was rejected by the patent examiner as anticipated or obvious over the Lever patents. (*See* TX 104 at KYP004-000430-

32).

194. In response, Kyowa limited the claims to olopatadine, and asserted unexpected results over the Wellcome Compounds disclosed in the Lever patents. (TX 105 at KYP004-000408-15). The '863 patent issued, and claims a pharmaceutical composition with an effective amount of olopatadine, referred to in the claims as the "cis isomer." (TX 6, col. 52, ll. 28-39; Bielory Tr. 1057:19-1058:9).

195. The '863 patent does not describe topical use, ophthalmic use, testing in human tissues, or testing on conjunctival mast cells in any species. (Bielory Tr. 1180:13-1181:8). Although the patent describes "injection" of olopatadine, the POOS would understand that an injection solution is not to be applied topically as an eye drop. (Abelson Tr. 1907:16-1908:1). The '863 patent does not describe or test a 0.1% w/v concentration of olopatadine. (Bielory Tr. 1183:16-18).

196. The '863 patent discloses data from only one test designed to test for anti-allergic properties – the rat PCA test. (Kaliner Tr. 600:15-601:24).

197. The '863 patent states that "PCA inhibiting activity is believed to be on the basis of an activity inhibiting liberation of chemical mediator such as histamine from fat skin cell." (TX 6, col. 27, ll. 63-65). The reference to "fat skin cell" refers to mast skin cells. (Kaliner Tr. 605:25-606:3).

198. As noted previously, the PCA test provides a general understanding of whether a compound impedes the allergic reaction, but it does not indicate the mechanism of action by which a compound inhibits the allergic reaction. (Kaliner Tr. 601:14-

603:9, 603:24-604:8; Abelson Tr. 1766:24-1767:8; *see also* Bielory Tr. 1183:21-1184:15 (PCA test "does not allow a researcher to differentiate amongst the various potential mechanisms of action that could have led to the inhibition of the allergic reaction.")).

199. Both Alcon's and Apotex's experts agree that the POOS would recognize that the statement regarding mast cell stabilization is an incorrect interpretation of the data. (Bielory Tr. 1184:21-1185:11; Kaliner Tr. 605:24-606:20; Abelson Tr. 1767:11-22).

200. The '863 patent does not teach the POOS that olopatadine would be effective as a mast cell stabilizer in human tissues, including the conjunctiva. (Kaliner Tr. 607:3-17; Abelson Tr. 1767:23-1768:18). Moreover, the '863 patent does not teach the POOS that olopatadine would stabilize mast cells in the human conjunctiva to a clinically relevant extent.

d. Ohmori Declaration

201. In connection with the prosecution of the '863 patent, Kenji Ohmori and Kyowa submitted a declaration (the "Ohmori declaration") to the patent examiner. (TX 14).

202. The Ohmori declaration was submitted to show that olopatadine (referred to as "Compound A") was superior to two structurally related compounds disclosed in

the Lever patents, Wellcome Compounds I and II.[4] Wellcome Compounds I and II are the closest prior art compounds to olopatadine. (TX 105 at KYP004-000415-16; Smith Tr. 1307:12-1308:2).

203. The Ohmori declaration reported the results of testing olopatadine and the Wellcome Compounds through the utilization of two *in vivo* models of anaphylaxis, PCA assay in rats and the passive anaphylactic bronchoconstriction assay[5] in guinea pigs. (TX 14 at 2-4).

204. Neither the rat PCA test nor the guinea pig bronchoconstriction assay address whether a compound works through mast cell stabilization. (Kaliner Tr. 603:24-604:8, 609:9-21; Abelson Tr. 1910:4-10 (PCA), 1911:13-17 (bronchoconstriction)).

205. Thus, the Ohmori declaration does not teach that olopatadine is a mast cell stabilizer or a human conjunctival mast cell stabilizer to a clinically relevant extent. (Kaliner Tr. 622:22-623:16; Abelson Tr. 1912:18-21).

---

[4] Wellcome Compounds I and II are two of the compounds exemplified in the Lever patents. The patent is named after the first named inventor on the patent, O. William Lever. The assignee of the patent is the Burroughs Wellcome Company. (Kaliner Tr. 709:4-9; Bielory Tr. 1092:1-6). Wellcome Compound I is Alcon's internal designation for (Z)-11-(3-dimethylaminopropylidene)-6, 11-dihydrobenz[b,e]oxepin-2-carboxylic acid and is Compound B in the '805 patent. Wellcome Compound II is Alcon's internal designation for (Z)-11-(3-dimethylaminopropylidene)-6, 11-dihydrobenz[b,e]oxepin-2-acrylic acid and is Compound C in the '805 patent. (*See* Docket # 173, ¶¶ 18-19).

[5] A bronchoconstriction assay is a histamine challenge model that measures histamine-induced reactions in an animal's lung. (Bielory Tr. 1193:9-12; Kaliner 608:21-24, 609:12-14, 609:18-19). Thus, "it is a way of looking at antihistamine activity." (Kaliner Tr. 609:14).

206. Moreover, the Ohmori declaration does not discuss topical, or ocular, application of olopatadine, and thus, does not teach these applications. (Kaliner Tr. 623:17-22).

e. The Ohshima Paper

207. In 1992, Etsuo Ohshima *et al.* published a paper entitled "Synthesis and Antiallergic Activity of 11-(Aminoalkylidene)–6-11-dihydrobenz[b,e]oxepin Derivatives" ("Ohshima paper"). (TX 15A). The authors of Ohshima included some of the inventors listed on the '863 patent. (TX 6; TX 15A; Kaliner Tr. 614:5-7).

208. The Ohshima paper was published five years after the '863 patent was filed. (TX 15A; Kaliner Tr. 613:16-614:11).

209. The Ohshima paper was considered by the patent examiner that allowed the '805 patent. (TX 4 at ALP001-042101).

210. Like the Ohmori declaration, the Ohshima paper reports data on a rat PCA test and on a guinea pig bronchoconstriction assay. (TX 15A at 2079; Kaliner Tr. 608:2-24; Bielory Tr. 1192:12-25).

211. Ohshima reported that "[a]mong the compounds tested, 15 and 16 [olopatadine and its E-isomer] are the most promising." (TX 15A at 2080).

212. Ohshima also reported that "[i]n the PCA test these compounds were approximately 100-200-fold more potent than 2 (ketotifen) . . . ." (TX 15A at 2080).

213. As stated previously, the PCA test and the bronchoconstriction test do not address whether a compound works through mast cell stabilization. (Kaliner Tr. 603:24-604:8, 608:2-609:21; Bielory Tr. 1192:12-1193:14).

214. The Ohshima article also states that "[olopatadine's] mechanism of action is now under extensive investigation in our research laboratories and a detailed pharmacological profile will be published." (TX 15A at 2080).

215. The POOS would understand from the statement above, and from the data, that olopatadine had an antihistaminic effect, but would not understand that olopatadine was a mast cell stabilizer. (Kaliner Tr. 613:7-13, 615:1-12; *see also* Bielory Tr. 1191:1-1192:5, 1196:2-6 ("Q: And you would agree with me, Doctor, that none of the data in the Ohshima article shows that olopatadine is a mast cell stabilizer, as opposed to having some other mechanism of action, correct? A: There's nothing that speaks toward or against it."); Abelson Tr. 1781:17-21-1782:1).

216. The Ohshima paper does not discuss topical application of olopatadine. (Kaliner Tr. 618:6-8). The Ohshima article does not discuss ophthalmic application of olopatadine. (Kaliner Tr. 618:9-10).

217. The POOS would have understood that the Ohshima paper does not teach that olopatadine would be a mast cell stabilizer, nor teach that olopatadine would be a human conjunctival mast cell stabilizer to a clinically relevant extent. (Kaliner Tr. 613:11-13).

f. Ishii Abstract

218. The Ishii abstract, entitled "Pharmacological Properties of a New Antiallergic Agent KW-4679," was published in 1988 and is prior art to the '805 patent. (TX 17 at AI007300).

219. The Ishii abstract was not disclosed to the PTO during the prosecution of the '805 patent. (TX 17 at AI007302; Bielory Tr. 1085:9-21; TX 4).

220. The Ishii abstract compared olopatadine with other known anti-allergy drugs – ketotifen, azelastine, oxatomide, and tranilast. (TX 17 at AI007302).

221. The abstract reported that "[o]ral administration of KW-4679 [olopatadine] at a dose of 0.01 mg/kg or higher showed inhibitory effects on the 48 hr. homologous passive cutaneous anaphylaxis in rats and the passive anaphylaxis bronchoconstriction in guinea pigs." (TX 17 at AI007302). The abstract also reported that "intravenous injection of KW-4679 after the maximum development of antigen-induced constriction of the airways resulted in a rapid dilation. . . . From these results KW-4679 is suggested to be a new potent antiallergic agent with a prolonged duration of action." (TX 17 at AI007302).

222. The data from the Ishii abstract does not teach that olopatadine had mast cell stabilizing effects. (Kaliner Tr. 625:6-16; Abelson Tr. 1771:23-1772:7).

223. The Ishii abstract does not teach the POOS that olopatadine would work as a mast cell stabilizer, nor as a mast cell stabilizer to a clinically relevant extent. (Kaliner Tr. 625:21-23).

224. The Ishii abstract does not discuss topical or ophthalmic use of olopatadine. (Kaliner Tr. 625:18-20; Abelson Tr. 1771:17-22).

g. Ohmori Abstract

225. The Ohmori abstract, entitled "Immunopharmacological Properties of a New Antiallergic Agent KW-4679," was prior art to the '805 patent. (TX 29 at AI007299).

226. The Ohmori abstract was not disclosed to the PTO during the prosecution of the '805 patent. (TX 4; Bielory Tr. 1087:7-11).

227. Like the Ishii abstract, the Ohmori abstract describes testing with olopatadine administered orally to guinea pigs and rats. (TX 29 at AI007299).

228. The Ohmori abstract reports data from a Compound 48/80 rat lethality assay. (TX 29 at AI007299). Compound 48/80 is a chemical – "a highly charged molecule" – that activates mast cells in a manner different than an antigen. (Kaliner Tr. 629: 18-630:10). The compound 48/80 test is based on a non-immunological method of causing mediator release from mast cells, and would therefore be understood by the POOS not to indicate whether a compound would stabilize mast cells in the face of an allergen challenge. (Kaliner Tr. 630:11-20). Thus, the test does not show whether a compound is a mast cell stabilizer in humans. (Abelson Tr. 1773:9-1775:3; Kaliner Tr. 626:14-21).

229. The Ohmori abstract does not teach the POOS that olopatadine would work as a mast cell stabilizer, nor as a mast cell stabilizer to a clinically relevant extent.

(Abelson Tr. 1775:8-14; Kaliner Tr. 626:14-18).

230. The Omhori abstract does not discuss topical or ophthalmic use of olopatadine. (TX 29 at AI007299).

h. The Lever '892 Patent

231. The Lever patent, entitled "Tricyclic Aromatic Compounds," issued in 1990 and is prior art to the '805 patent. (TX 21A).

232. The Lever patent was considered by the patent examiner who approved the '805 patent. (TX 4 at ALP001-042030).

233. The Lever patent describes a generic formula of chemical compounds, termed formula (I). (TX 21A, col. 1, ll. 27-46). Formula (I), as disclosed in claim 1, potentially embraces millions of different compounds. (Bielory Tr. 1196:22-1197:14; Abelson Tr. 1775:22-25).

234. Claim 1 of the Lever patent claims:

> 1. A method of treating allergy in a mammal which comprises administering to a mammal in need thereof an effective allergy treatment amount of a compound of formula (I) or a pharmacologically or pharmaceutically acceptable salt thereof; wherein R^1 is $-CH_2-O-$, R^2 and R^3 are the same or different and are each hydrogen or C_{1-4} alkyl, R^4 is a C_{1-2} bivalent hydrocarbon group and is joined to the aromatic ring system at the 2 position and n is 2.

(TX 21A, col. 19, ll. 35-53).

235. Dependent claim 2 of the Lever patent claims:

> 2. The method of claim 1 in which R^2 and R^3 are methyl.

(TX 21A, col. 19, ll. 54-55).

236. Dependent claim 5 of the Lever patent claims:

> 5. The method of claim 4 in which R^2 and R^3 are methyl.

(TX 21A, col. 20, ll. 21-22). Claim 4 of the Lever patent is directed to a "method of treating asthma," but in all other respects, is verbatim of claim 1. (*Compare* TX 21 A, col. 20, ll. 3-12 (claim 4), *with* TX 21A, col. 19, ll. 35-53 (claim 1)).

237. Although olopatadine is not specifically described in the patent, it falls within the broad chemical description of compounds claimed and is one of not more than 16 compounds whose use is claimed in claims 2 and 5. (Abelson Tr. 1776:1-3; Docket # 179, Stipulation ¶ 2).

(1) Lever Is Not Addressed to Olopatadine

238. The specific chemical formula for olopatadine is not set forth anywhere in the Lever patent. (Abelson Tr. 1776:5-7; Bielory Tr. 1199:20-1200:1).

239. Olopatadine is not described in any of the examples of the Lever patent. (*See infra* Finding of Fact § VI.A.2.h(3)).

240. None of the testing described in the Lever patent involved olopatadine. (Bielory Tr. 1200:2-3 (no data on olopatadine in the Lever patent), 1204:17-19; Kaliner Tr. 628:4-14; Abelson Tr. 1776:11-12).

241. There is no description in Lever of how to make olopatadine. (Bielory Tr. 1200:12-16). Indeed, both sides' experts agree that nothing in the Lever patent indicates that the inventors had even synthesized olopatadine. (Abelson Tr.

1776:25-1777:3; Bielory Tr. 1200:12-16).

242. The Lever patent expressly discloses "preferred" and "most preferred" compounds of formula (I) in the specification. (TX 21, col. 1, l. 47-col. 2, 1.5). Olopatadine is not included in that disclosure. (Bielory Tr. 1197:22-1198:2, 1198:13-15; Kaliner Tr. 634:14-23; Abelson Tr. 1776:11-17).

243. Nothing in the claims of the Lever patent point the POOS to olopatadine as opposed to the many other compounds encompassed in those claims. (Bielory Tr. 1232:24-1233:7; *see also infra* Finding of Fact § VI.A.2.h(5)).

244. Based on the lack of description or testing of olopatadine in the Lever patent, the POOS would not regard the Lever patent as being addressed to olopatadine or its pharmacological properties. (Abelson Tr. 1777:4-13).

(2) Column 5 of Lever Does Not Teach Stabilizing Mast Cells in the Human Conjunctiva

245. In column 5 of the specification, the authors of the Lever patent describe two categories of compounds – one having mast cell stabilizing and antihistaminic properties to be used primarily for asthma, and a second having only antihistaminic properties to be used for treating allergic conditions such as allergic conjunctivitis. (Kaliner Tr. 636:8-637:22; Abelson Tr. 1778:21-1779:24). Column 5 of the Lever patent reads, in relevant part:

> The compounds of this invention having antiallergic activity may be used for the same indications as clinically used antiasthmatic compounds, namely to help control bronchoconstriction or bronchospasm characteristic of

> allergic asthma and exercise induced asthma. . . . The compounds are believed to inhibit the release of autacoids (i.e. histamine, seratonin and the like) from mast cells and to inhibit directly the antigen-induced production of histamine. Thus, they may be classified as mast cell stabilizers with antihistaminic action.
>
> The compounds of this invention having antihistamine activity may be used for the same indications as clinically used antihistamines, namely to relieve detrimental symptoms (caused by histamine release) of nasal stuffiness due to colds and vasomotor rhinitis and for the symptomatic control of allergic conditions including . . . allergic conjunctivitis . . . .

(TX 21A, col. 5, ll. 21-40).

246. Read together, these two paragraphs from column 5 teach the POOS that to the extent any of the compounds of formula (I) are considered to be mast cell stabilizers, they would be useful for the treatment of asthma, not allergic conjunctivitis. (Kaliner Tr. 637:16-22; Abelson Tr. 1779:13-19). The POOS would not believe that Lever was suggesting that the compounds of this invention could be used to treat allergic conjunctivitis through mast cell stabilization. (Abelson Tr. 1779:20-24).

(3) Lever Does Not Teach the Use of Olopatadine at 0.1% w/v

247. The Lever patent "provides pharmaceutical formulations, both for veterinary and human use, which comprise a compound of formula (I) together with one or more pharmaceutically acceptable carriers therefore and optionally any other pharmaceutically therapeutic ingredients." (TX 21A, col. 6, ll. 14-19).

248. The Lever patent provides that one exemplary formulation applicable to the compounds disclosed in the Lever patent is an ophthalmic solution as follows:

> Nasal spray formulations comprise purified aqueous solutions of the active compound with preservative agents and isotonic agents. Such formulations are adjusted to a pH and isotonic state compatible with the nasal mucous membranes.
>
> Ophthalmic solutions are prepared by a similar method to the nasal spray except that the pH and isotonic factors are adjusted to match that of the eye.

(TX 21A, col 7, ll. 7-16).

249. Example 8 discloses ten exemplary formulations, which it labels (A)-(J). (*See* TX 21A, col. 17, l. 20 – col. 19, l. 34).

250. The first sentence of Example 8 defines the active compound as "(Z)-11-(3-(dimethylamino)-propylidene)-6, 11-dihydrodbenz[b,e]oxepin-2-carboxylic acid, i.e., Compound 1." (TX 21A, col. 17, ll. 23-25).

251. Compound 1 is not olopatadine. (Kaliner Tr. 641:25-642:22).

252. Each of the formulations (A) through (J) in Example 8 incorporate the "Active Compound," i.e., Compound 1. (Kaliner Tr. 640:5-641:8).

253. Example 8(G) refers to the preparation of a syrup "containing other active ingredients *in addition to* a compound of formula (I)." (TX 21A, col. 18, ll. 40-57) (emphasis added).

254. Example 8(I) refers to the preparation of an ophthalmic solution, and includes a table that describes an ophthalmic formulation containing the active compound at

0.1g/100mL, or 0.1% w/v. (*See* TX 21A, col. 19:5-10).

255. Example 8(G)'s reference to "other active ingredients in addition to a compound of formula (I)" does not change the definition of "Active Compound" in Example 8, and more particularly, the definition of "Active Compound" for purposes of the ophthalmic solution referenced in Example 8(I). (Kaliner Tr. 640:5-641:8). The POOS would understand that Example 8(G) uses Compound 1, just as all of the other examples do. (Kaliner Tr. 640:5-15; Abelson Tr. 1780:13-18).

256. Moreover, Apotex's interpretation of Example 8(G) contradicts the teachings of the Lever patent. Formula (I) includes millions of compounds. (Bielory Tr. 1196:22-1197:14; Abelson Tr. 1775:22-25). The POOS would not interpret "Active Compound" in Example 8(I) to refer to these millions of compounds. Indeed, the POOS would understand that one could not change the active ingredient without needing to reassess what the appropriate formulation and concentration would be for that compound. (Kaliner Tr. 641:25-642:22). As even Apotex's expert concedes, the Lever patent itself teaches that "[t]he amount of active compound, i.e., a compound of formula (I) required for use in the above conditions will vary with the compound chosen, the route of administration and the condition and mammal undergoing treatment, and is ultimately at the discretion of the physician." (TX 21A, col. 5, ll. 57-62; Kaliner Tr. 642:6-22; Bielory Tr. 1219:1-12; Abelson Tr. 1931:10-1932:17). In other words, the POOS would understand that one could not simply substitute one active ingredient for another in

the formulation without adjusting the amount of concentration of active ingredient to be used. (Kaliner Tr. 642:6-22; Abelson Tr. 1781:1-11, 1930:18-1931:9). Thus, Lever does not teach the use of olopatadine at 0.1% w/v.

(4) The Data in Lever Does Not Teach Human Conjunctival Mast Cell Stabilization

257. The Lever patent contains no data directed to identifying whether any of the compounds tested works as a mast cell stabilizer. (Kaliner Tr. 632:5-14; Abelson Tr. 1777:14-17).

258. The Lever patent contains no data regarding testing on human tissues or conjunctival tissues of any species. (Bielory Tr. 1204:3-8).

259. Lever contains data regarding antihistamine activity in guinea pigs (Example 7(a) and 7(b)), and a Compound 48/80 anaphylaxis test in rats (Example G). (TX 21A, col. 15, l. 35 - col. 17, l. 18). These tests, for the reasons explained numerous times before, do not allow the POOS to determine whether a compound is working as a mast cell stabilizer.

(5) Claims 2 and 5 of Lever Do Not Teach Human Conjunctival Mast Cell Stabilization

260. Although the methods of claims 2 and 5 of the Lever patent employ one of no more than 16 compounds of which olopatadine is one, nothing in these claims points the POOS to olopatadine as opposed to one of the other compounds covered by those claims. (Bielory Tr. 1232:24-1233:7).

261. As noted above, the Lever patent mentions mast cell stabilization in the context of

treating asthma, and claim 5 is directed to a "method of treating asthma." (TX 21A, col. 20, ll. 3-22).

262. There is no data to support an assertion that some of the Lever compounds act through mast cell stabilization. (Kaliner Tr. 632:5-14; Abelson Tr. 1778:10-12; Bielory Tr. 1215:1-14). The POOS would therefore find the statement regarding treating asthma with a mast cell stabilizer as speculation and therefore give it no weight. (Abelson Tr. 1778:13-20; Kaliner Tr. 606:15-20 (the POOS would disregard statements unsupported by data)).

263. The genus of compounds described in claim 2, which discusses methods of treating allergy in a mammal, is very broad. As both sides' experts agree, this claim is directed to a huge number of possible methods. (Kaliner Tr. 659:12-22; Bielory Tr. 1233:8-13).

264. For example, in addition to any one of not more than 16 different compounds, the method of claim 2 could employ any number of methods of treating allergy, in any number of tissues, in any number of mammals, at any number of effective treatment amounts. (Kaliner Tr. 658:10-659:11; Bielory Tr. 1233:8-1235:19). Adding all of those possible variables, the number of permutations is nearly countless. (Kaliner Tr. 659:12-15). Claim 2 is consequently "quite expansive," according to Apotex's expert, Dr. Bielory. (Bielory Tr. 1233:8-13 (testifying that claim 2 is "quite expansive")).

265. The same is true with respect to the huge number of variations covered by claim 5

of the Lever patent. (Kaliner Tr. 659:16-22).

266. In essence, claims 2 and 5 of Lever do not change the fundamental teaching of the Lever patent to the POOS. (Kaliner Tr. 658:4-6).

(6) Lever Does Not Teach Other Elements of the '805 Patent

267. The Lever patent does not teach the other elements of the '805 patent. For example, it does not teach that olopatadine could be used in a topical formulation (Kaliner Tr. 642:23-25); it does not describe the use of olopatadine in a method of treating allergic eye disease in humans (Kaliner Tr. 656:17-19; Abelson Tr. 1782:7-15); it does not teach that olopatadine would be a therapeutically effective mast cell stabilizer at 0.1% (Kaliner Tr. 643:6-8); and it does not describe a composition containing an amount of olopatadine falling within any of the concentration ranges of claims 2-4 or 6-8 of the '805 patent.

i. The Berdy & Abelson Article

268. The Berdy & Abelson article, entitled "Allergic Conjunctivitis: A Survey of New Antihistamines," was published in 1991 and is prior art to the '805 patent. (TX 713). One of the authors of this article is Dr. Mark Abelson ("Dr. Abelson"), an expert employed by Alcon. (TX 1795:25-1796:2).

269. The objective of the study "was to determine the therapeutic value of a wide variety of H_1antihistamines for potential ophthalmic use by performing toxicity and efficacy tests in rabbits and humans." (TX 713 at AI008036).

270. The authors stated that "[t]he results of the study suggest that 0.1%, 0.2%, and 0.3% chlorpheniramine, 0.3% dexbrompheniramine, 0.2% pyrilamine, and 0.4% and 0.5% pheniramine were effective in relieving the itching and conjunctival injection associated with topically applied histamine." (TX 713 at AI008036).

271. Dr. Abelson testified that the purpose of the study was to determine an appropriate dose range, and not the compound's mechanism of action. (Abelson Tr. 1805:20-21, 1902:5-6, 1902:20-21 (testifying that the study was not about mast cell stabilization)).

272. The POOS would not reasonably expect that because a compound is effective as an oral antihistamine, that it could be formulated or useful as a topical eye drop. (Abelson Tr. 1900:24-1901:3). In fact, at the time of the study, out of "a very large number of antihistamines" that were known at the time, only three had been formulated into ophthalmic preparations and sold as such. (Abelson Tr. 1899:2-9).

273. Table 1 of the Berdy & Abelson article lists well-known antihistamines. (TX 713 at AI008038). Only two of them had been made into topical ocular formulations. (TX 713 at AI008038; Abelson Tr. 1899:13-1900:7).

3. The Prior Art Taught Away From the Claimed Invention

274. Based on the teachings of the prior art, the POOS would not have been motivated to select olopatadine as a mast cell stabilizer. (Abelson Tr. 1784:20-24).

275. Nothing in the prior art suggested or demonstrated that olopatadine could stabilize mast cells in any animal or human mast cell population.

276. Given mast cell heterogeneity, even if the prior art demonstrated stabilization of animal mast cells, that would not have given the POOS a reasonable expectation that olopatadine would stabilize human conjunctival mast cells. (Abelson Tr. 1753:12-1754:4; *see, e.g.*, Kaliner Tr. 607:10-17).

277. Both Hamilton and Kamei, the closest prior art to the '805 patent, taught away from the present invention by showing that olopatadine was not effective as a mast cell stabilizer in those models. (Abelson Tr. 1783:7-22, 1933:13-25).

278. The prior art did not disclose the use of 0.1% w/v concentration of olopatadine, nor the use of 0.1% w/v of olopatadine in the human eye as a mast cell stabilizer.

279. The prior art taken as a whole would have not motivated the POOS to use olopatadine to stabilize human conjunctival mast cells at 0.1% w/v. (Kaliner Tr. 655:6-11).

4. Differences Between the Claimed Invention and the Teachings of the Prior Art

a. The Prior Art Does Not Suggest Using Olopatadine to Treat Allergic Eye Disease in Humans Through Mast Cell Stabilization

280. As discussed at length above, the prior art did not teach or suggest using olopatadine, let alone a 0.1% olopatadine ophthalmic solution, to treat allergic eye disease through mast cell stabilization. Not only did the prior art fail to suggest that olopatadine would be a clinically effective human conjunctival mast cell stabilizer, but the closest prior art taught away from the notion that olopatadine is a

mast cell stabilizer at all.

b. The Prior Art Does Not Teach That Olopatadine Would Be Effective as a Topical Ocular Treatment for Human Use

(1) Apotex Failed to Adduce Evidence that the POOS Would Have Selected Olopatadine From the Many Compounds Then Under Study

281. During the mid-1990s, there were hundreds of compounds being studied as anti-allergic compounds. (Abelson Tr. 1749:16-1751:12). Thousands of journal articles were written reporting the general anti-allergic effects of these compounds. (Abelson Tr. 1749:16-1751:12). One could not predict that any one of these compounds would be successful.

282. Apotex failed to introduce any evidence to show that among all of the compounds being studied, the POOS would have focused on olopatadine.

(2) That Olopatadine Showed Effect as an Oral Antihistamine Would Not Suggest It Could Be Developed as a Topical Ophthalmic Preparation

283. Olopatadine was tested and discussed in the prior art, most notably in Hamilton, Kamei, the Oshima paper, and the Ishii abstract. At most, these references showed that olopatadine had some effect as an oral antihistamine.

284. These references would not give the POOS a reasonable expectation that a compound that was effective as an oral antihistamine could be formulated or useful as a topical ophthalmic preparation. (Abelson Tr. 1900:20-1901:3). For example, as noted above, many oral antihistamines cannot be formulated as topical solutions

for the eye. (Abelson Tr. 1901:8-1902:2; TX 713 at AI008038). By the mid-1990s, there were many antihistaminic compounds that were extremely successful as oral antihistamines, almost none of which had been developed as topical ocular treatments. (Abelson Tr. 1900:5-19; TX 713 at AI008038).

285. Nor would Kamei, the only prior art testing of olopatadine in the eye of any species, provide the POOS with an expectation that olopatadine could be formulated as an effective treatment in the human eye. (Kaliner Tr. 734:7-735:12). The test subjects in Kamei were guinea pigs, which are not used to test whether a compound is safe for the human eye. (Abelson Tr. 1904:18-1905:4).

286. Based on the prior art as a whole, including Kamei, the POOS would not reasonably expect that olopatadine could be formulated for non-toxic application to the human eye.

5. Objective Indicia of Nonobviousness

287. Patanol® is Alcon's 0.1% olopatadine ophthalmic product and is a commercial embodiment of claims 1-8 of the '805 patent. (Kaliner Tr. 561:1-14; Abelson Tr. 1736:14-17; TX 3A).

a. Long-Felt Need and Failure of Others

288. By the mid-1990s, there was a long-felt need for an effective mast cell stabilizer for the human eye. (Abelson Tr. 1732:7-17).

289. Although it was known as a mast cell stabilizer, cromolyn had been found to be ineffective in the human eye. (Abelson Tr. 1733:21-1734:8). Cromolyn was not

effective in laboratory testing as a stabilizer of MCTC cells, which make up all or nearly all of the mast cells in the conjunctiva. (Bielory Tr. 1145:2-6 (cromolyn ineffective), 1052:16-18 (MCTC cells predominate in the conjunctiva); Abelson Tr. 1764:20-23).

290. Research companies had been looking for a better mast cell stabilizer than cromolyn since the 1970s, and were spending millions to find such a compound. (Bielory Tr. 1143:7-1144:9).

291. These efforts were a failure: no company had been successful by the mid-1990s in finding an effective human conjunctival mast cell stabilizer. (Abelson Tr. 1736:10-13). The reliance on animal models had frustrated these companies' research efforts – compounds that appeared to be effective in animal models turned out not to be effective in human models. (TX 219; Yanni Tr. 142:23-144:2).

292. Patanol® was the first product that was effective as a mast cell stabilizer in the human eye. (Abelson Tr. 1736:14-17).

293. Patanol® satisfied a long-felt need by providing proven mast cell stabilization for the human eye, and is clinically successful as a result. (Abelson Tr. 1745:9-24).

b. Clinical and Commercial Success

294. Patanol® has been shown to be clinically superior to all other methods of treating allergic eye disease; it relieves all of the symptoms of allergic conjunctivitis, and it significantly reduces or prevents future symptoms. (Abelson Tr. 1741:25-1745:7). Patanol® has revolutionized the market by providing highly efficacious treatment

for a broad range of patients and conditions. (Kaliner Tr. 503:8-23; Abelson Tr. 1745:1-7).

295. The superior effectiveness of Patanol® has been recognized by doctors and patients, and Patanol® is the gold standard for treatment of allergic eye disease. (Abelson Tr. 1745:1-7).

296. Patanol® has been shown in repeated clinical studies to be highly effective, safe, and comfortable. (Abelson Tr. 1741:25-1744:14; Kaliner Tr. 543:16-551:24; TX 703; TX 706A; TX 708; TX 714; TX 715; TX 718; TX 726; TX 732A; TX 735; TX 736; TX 749; TX 792).

297. Patanol® was launched in 1997. (Warner Tr. 1432:10-12). It received a phenomenal reception from physicians and patients immediately upon launch. (Warner Tr. 1435:16-1436:17). Within just a few months of launch, Patanol® became the top selling product in the category. (Warner Tr. 1441:4-1442:21; TX 795).

298. Patanol® has been an outstanding commercial success. (Warner Tr. 1446:9-22).

299. Patanol® was one of the fastest products ever to sell $50 million per year for Alcon. (Warner Tr. 1445:12-18).

300. Patanol® achieved a nearly 70% market share by 1999, two years after launch. (Warner Tr. 1449:2-13). Patanol® maintained approximately a 70% market share through 2006. (Warner Tr. 1449:2-16; AA-37).

301. Even today, thirteen years after launch, Patanol® is the market leader for

prescription allergy products. (Warner Tr. 1488:5-15).

302. Patanol® has maintained this market dominant position despite the presence of major competitors like Allergan, Bausch & Lomb, Johnson & Johnson, and others. (Warner Tr. 1449:25-1450:17).

303. In 2006 alone, Patanol® sold more than $300 million in prescriptions. (Warner Tr. 1447:8-10; TX 112; AA-36).

304. By mid-2007, the ten-year total of Patanol® sales in the United States was nearly $2 billion, and sales to date have exceeded that number. (Warner Tr. 1446:23-1447:7; TX 112; AA-36).

305. The market for treating seasonal allergic conjunctivitis has grown dramatically since Patanol® came on the market, primarily due to the invention of Patanol®. (Warner Tr. 1454:10-1455:14). Prescriptions for allergy eye drops have increased from 1.5 million at the time of Patanol®'s introduction in 1997 to almost 6 million in 2006. (Warner Tr. 1454:23-1455:14; AA-38).

c. Industry Praise

306. Patanol® has been subject to wide-spread praise within the industry. Immediately upon its launch, doctors were impressed with its performance and commented on its efficacy. (Warner Tr. 1435:16-1437:24). Patanol® was lauded for quickly achieving a market leader position. (TX 795 ("Alcon's starry-eyed hopes for its chronic conjunctivitis drug Patanol are paying off . . . .").

d. Unexpected Results

(1) Patanol® Effectively Stabilizes Human Conjunctival Mast Cells and Is Not Biphasic

307. The POOS would not have expected olopatadine to be an effective mast cell stabilizer in the human eye based on available data. (Abelson Tr. 1783:23-1784:5). To the contrary, the POOS in 1995 would have expected olopatadine to be biphasic based upon its profile as an antihistamine. (Kaliner Tr. 536:3-537:11; Bielory Tr. 1236:13-24).

308. Patanol® is unexpectedly effective as a mast cell stabilizer in the human eye. (Kaliner Tr. 535:16-536:8). Olopatadine exhibits a therapeutic plateau in dose response studies of mast cell stabilization that would not have been expected in the mid-1990s. (Abelson Tr. 1790:24-1791:22; Kaliner Tr. 535:16-536:8). For example, given that azelastine, epinastine, ketotifen, and levocabastine all have an extremely narrow range of concentrations at which they prevent mediator release, and that at very slightly higher concentrations they cause mediator release, it is not possible to achieve a dose at which these compounds could effectively stabilize mast cells in the human eye. (Kaliner Tr. 542:5-13; AA-16.01-.02; TX 784 at ALP002-001040; Abelson Tr. 1789:16-1790:2). By contrast, olopatadine has a very wide range of concentrations at which it is an effective conjunctival mast cell stabilizer. (Kaliner Tr. 542:5-15; AA-16.01-.02; TX 784 at ALP002-001041). This effective concentration range occurs at a higher concentration that allows it to

penetrate the conjunctival membrane and be effectively delivered to the mast cells. (Kaliner Tr. 530:17-532:14; AA-16.01-.02; TX 784).

309. Relatedly, Patanol® is unexpectedly not biphasic. (Kaliner Tr. 535:16-536:8; TX 227). Other than products containing olopatadine, all products available for the treatment of allergic eye disease that have an antihistaminic effect are biphasic, making solutions containing olopatadine unique in this regard. (Yanni Tr. 171:10-172:2; Kaliner Tr. 536:3-8, 538:1-539:1; AA-16.01-.02).

310. By 2003, Dr. Yanni had tested approximately 300 compounds in the HCMC assay, but had not found an effective human conjunctival mast cell stabilizer other than olopatadine. (Yanni Tr. 191:22-192:9). All of the antihistamines tested were biphasic with the exception of olopatadine. (Yanni Tr. 192:10-15). Tests done using red blood cells and artificial membranes show that olopatadine does not have the same lipid-lipid interaction with the cell membrane that other antihistamines such as ketotifen have. (Kaliner Tr. 536:9-25; TX 227). Therefore, olopatadine does not make the membrane rigid or cause cell lysis as biphasic antihistamines do. (Kaliner Tr. 536:20-25; TX 227 at 13-14). This finding would be totally unexpected to the POOS. (Kaliner Tr. 537:1-14; TX 227).

311. Products available for treating allergy, other than products containing olopatadine, have clinical outcomes consistent with antihistamines, in that they block itching, but do not block other signs and symptoms of allergic conjunctivitis. (Kaliner Tr. 541:18-542:4). Azelastine, epinastine, ketotifen, and levocabastine are not acting

as mast cell stabilizers in the human eye; they are acting as antihistamines. (Kaliner Tr. 542:16-22; AA-16.01-.02; TX 784 at ALP002-001040, 41).

312. Apotex repeatedly claimed throughout the trial that ketotifen was not only a potent antihistamine, but also a known mast cell stabilizer. In support of this proposition, Apotex introduced into evidence a 2003 article entitled "In vitro Inhibition of Human Conjunctival Mast Cell Degranulation by Ketotifen" by C. Schoch (the "Schoch article") as evidence that ketotifen directly and effectively stabilized human conjunctival mast cells, even though it exhibited a biphasic effect *in vitro*. (TX 445).

313. Not only is the Schoch article not prior art to the '805 patent, the data in the article is not credible. (Kaliner Tr. 752:8-18; TX 445). It purports to show ketotifen is stabilizing conjunctival mast cells at levels that are a million times less than clinically used concentrations, which is "an unbelievable claim." (Kaliner Tr. 752:8-18). Moreover, the Schoch article confirms that ketotifen exhibits a biphasic effect and could not be dosed topically at the concentrations where it purportedly stabilizes mast cells. (TX 445; Kaliner Tr. 752:22-753:12).

314. Apotex also introduced into evidence a 2005 patent application filed by Dr. Abelson entitled "Novel Topical Ophthalmic Formulations," wherein the patent states that ketotifen is "a pharmaceutical agent having antihistamine, mast-cell stabilizing and anti-inflammatory properties." (TX 602 at DTX602-0004 ¶ 5). The patent application does not mention that ketotifen has a biphasic effect.

315. Claim 16 of the patent application claims a method wherein "the antiallergenic agent is a drug with multiple modes of action," which, according to Claim 15, "consists of: an antihistamine, a mast cell stabilizer, a drug with multiple modes of action and a NSAID." (TX 602 at DTX0602-0011). Claim 17 claims that the drug "with multiple modes of action is ketotifen fumarate." (TX 602 at DTX0602-0011).

316. Dr. Abelson testified that he described ketotifen as a mast cell stabilizer because "ketotifen and azelastine and cromolyn and Alamast . . . and [o]lopatadine . . . are all assigned to that category . . . based on the animal data to this category." (Abelson Tr. 1892:16-24; *see also* Abelson Tr. 1894:4-5 ("ketotifen does have mast cell stabilizing properties in animals and other tissue")). He also testified that olopatadine has demonstrated mast cell stabilization as its mechanism of action, which makes it "unique." (Abelson Tr. 1892:25-1893:3). Moreover, the evidence overwhelmingly confirms that ketotifen is an antihistamine that exhibits the biphasic effect.

317. In sum, none of the available products that claim to act through mast cell stabilization (i.e., ketotifen, levocabastine, epinastine, and azelastine), with the exception of products containing olopatadine, had any data submitted to the FDA showing that they stabilized human conjunctival mast cells. (Kaliner Tr. 540:13-21). The pharmacological data on these products was based on animal and non-tissue specific mast cell testing. (Kaliner Tr. 540:13-21; Abelson Tr. 1914:14-25

(testifying that ketotifen was listed on the FDA-approved package insert as a mast cell stabilizer based on animal data, and thus, studies "haven't shown it to be a mast cell stabilizer in humans")).

(2) Olopatadine Is Unexpectedly Superior

318. As of the mid-1990s, one would not expect that olopatadine would be superior to other compounds, including the Wellcome compounds, with respect to human conjunctival mast cell stabilization. Yet, olopatadine has been shown to be superior as a mast cell stabilizer to all of the competitor compounds, and to the closest prior art compounds, the Wellcome compounds. (Yanni Tr. 191:17-253:21-269:6; Kaliner Tr. 538:3-539:1; Abelson Tr. 1790:24-1791:22; TX 206 at ALP013-120410; TX 206A at ALP013-120411; AA-16.01; AA-89.02).

319. Olopatadine's tremendous clinical success and efficacy could also not have been predicted in the mid-1990s. (Abelson Tr. 1790:24-1791:22). Because of its effect as a mast cell stabilizer, Patanol® has been a tremendous success in treating patients, becoming the gold standard. (Abelson Tr. 1744:25-1745:7). While traditional antihistamines treat only itching, Patanol® treats itching, swelling, irritation, tearing, and redness. (Kaliner Tr. 543:4-10; AA-96.01a-96.05a; TX 703; TX 706A; TX 708; TX 714; TX 715; TX 718; TX 726; TX 732A; TX 735; TX 736; TX 749; TX 792). Patanol® provides long-lasting effective treatment for patients. (Kaliner Tr. 543:23-544:9). Patanol® is more comfortable than comparator products. (Kaliner Tr. 544:25-545:5; TX 708). The result of these

characteristics is that patients are much more satisfied with the clinical results. (Kaliner Tr. 543:4-10). Patanol® has revolutionized the market by providing highly efficacious treatment for a broad range of patients and conditions. (Kaliner Tr. 503:8-23; Abelson Tr. 1744:25-1745:24). These effects could not have been predicted by the POOS as of 1995, when the human conjunctival mast cell stabilizing properties of olopatadine at 0.1% were unknown. (Abelson Tr. 1752:7-17).

B. Anticipation

320. Apotex contends that the Lever patent anticipates claims 1-8 of the '805 patent under 35 U.S.C. § 102, either explicitly or inherently.

1. Claims 1-8 of the '805 Patent Are Not Disclosed in the Lever Patent

321. Claim 1 of the '805 patent discloses the following elements: (1) a method of treating allergic eye disease in humans, (2) through the use of olopatadine or a pharmaceutically acceptable salt thereof, (3) by way of topical administration to the eye, (4) through the activity of stabilizing conjunctival mast cells. (*See* TX 3A, col. 7, ll. 27-34).

322. Claim 1 of the Lever patent discloses the following elements: (1) a method of treating allergy in a mammal, (2) which comprises administering to a mammal in need thereof, (3) an effective allergy treatment amount of a compound of formula (I) or a pharmacologically and pharmaceutically acceptable salt thereof, (4)

wherein R^1 is $– CH_2 – O –$, R^2 and R^3 are the same or different and are each hydrogen or C_{1-4} alkyl, R^4 is a C_{1-2} bivalent hydrocarbon group and is joined to the aromatic ring system at the 2 position and n is 2. (TX 21A, col. 19, ll. 35-53).

323. Claim 2 of the '805 patent is a dependent claim comprising all the elements of claim 1 discussed above with two additional limitations: (1) the composition "is a solution" and (2) the amount of olopatadine or a pharmaceutically acceptable salt thereof "is from about 0.0001 w/v % to about 5% (w/v)." (TX 21A at col. 7, ll. 35-39). Claims 3 and 4 of the '805 patent mirror claim 2 except that claims 3 and 4 limit the amount of olopatadine in the composition to about 0.001 to about 0.2% w/v, and about 0.1% w/v, respectively. (TX 21A at col. 7, l. 39 – col. 8, l. 3).

324. As noted previously, claim 2 of the Lever patent describes a general chemical formula that includes olopatadine; however it is not one of the "preferred" or "most preferred" compounds of formula (I) in the specification. (TX 21A, col. 1, ll. 47 – col. 2, ll. 35; *see also supra* Finding of Fact # 242).

325. Moreover, olopatadine is not otherwise referred to or specifically described in the Lever patent. (Bielory Tr. 1200:12-16). In fact, both sides' experts agree that nothing in the Lever patent indicates that the inventors had even synthesized olopatadine. (Abelson Tr. 1776:25-1777:3; Bielory Tr. 1200:12-16; *see also supra* Finding of Fact # 241).

326. The Lever patent, in column 5, teaches that to the extent any of the compounds of formula (I) are mast cell stabilizers, they would be useful for the treatment of

asthma, not allergic conjunctivitis. (TX21A, col. 5, ll. 21-40; *see also supra* Finding of Fact # 245).

327. The Lever patent teaches pharmaceutical formulations for human medical use, "which comprise a compound of formula (I) together with one or more pharmaceutically acceptable carriers . . . ." (TX 21A, col. 6, ll. 14-19). These pharmaceutical formulations are exemplified in Examples 8(A)-(J) of the Lever patent. (TX 21A, col. 17, l. 20 – col. 19, l. 34). The exemplary formulations define the active compound as Compound 1, which is not olopatadine. (*See supra* Findings of Fact ## 249-52).

328. Example 8(I) provides an exemplary ophthalmic formulation containing the "active compound" at 0.1% w/v. (TX 21A, col. 19, ll. 4-14). Again, the active compound is not olopatadine. (*See supra* Findings of Fact ## 254-55).

329. In addition, the Lever patent explains that "[t]he amount of active compound, i.e., a compound of formula (I) required for use in the above conditions *will vary with the compound chosen*, the route of administration and the condition and mammal undergoing treatment, and is ultimately at the discretion of the physician." (TX 21A, col. 5, ll. 56-58 (emphasis added). Thus, a person of ordinary skill in the art in 1995 would have understood that a therapeutically appropriate concentration of olopatadine would not necessarily be the same as the therapeutically effective concentration of other compounds within the Lever patent's formula (I), including Compound 1, because different compounds are effective at different

concentrations. (*See* Kaliner Tr. 641:25-642:22; *see also supra* Finding of Fact # 256).

330. Claims 5-8 of the '805 patent are dependent claims that stem from independent claim 1, and limit the method of claim 1 to compositions in which the active compound is the "Z isomer" "substantially free of" the "E isomer." (TX 3A at col. 8, ll. 4-22; *see also supra* Finding of Fact ## 146-47).

331. The Lever patent discloses that:

> The compounds of the present invention exist in either the cis (Z) or trans (E) isomers (in relation to the bridge oxygen in the case of formula (IIA) and the acid side chain in the case of formula (IIB)). If the compounds of formula (I) or (II) contain a double bond in the acid bearing side chain, i.e., R^4 or R^5, there exists a second possibility of Z and E isomeric forms. All such isomers and the isomeric mixture of these compounds are included within the scope of this present invention.

(TX 21A, col. 2, ll. 36-45).

332. The Lever patent does not describe the use of olopatadine, nor the use of the Z isomer (olopatadine) free of the E-isomer of olopatadine, to a particular level of purity. (*See supra* Findings of Fact § VI.A.2.h(1)).

333. Claims 6-8 of the '805 patent, like claims 2-4, specify particular concentrations of olopatadine. Indeed, they specify the exact same concentrations, including, *inter alia*, the use of olopatadine at 0.1% w/v. The only difference is that the concentration is "substantially free" of the E isomer. (TX 3A at col. 7, l. 35 – col. 8, l. 22; *see also supra* Finding of Fact # 147).

334. As noted above, the Lever patent does not describe a method for treating allergic eye disease in humans through the topical administration of 0.1% w/v of olopatadine, or any other concentration of olopatadine falling within any of the concentration ranges of claims 2-4 or 6-8 of the '805 patent, to stabilize human conjunctival mast cells. (Kaliner Tr. 657:24-658:3; Abelson Tr. 1783:1-5; *see also supra* Findings of Fact §§ VI.A.2.h(1), (3), (6)).

335. The PTO considered the Lever patent during prosecution of both the '805 patent and the prior abandoned application ('229 application) whose claims were broader than those of the '805 patent and never took the position that Lever anticipated the claimed invention in the '805 patent. (TX 4 at APL001-042082-087) (office action regarding the '729 application); TX 449 at ALP001-003032-033 (office action regarding the '227 application); Ryan Tr. 1607:14-1608:18 (no anticipation rejection over Lever in the '805 application); Ryan Tr. 1565:24-1566:11 (no anticipation rejection regarding the '227 application).

336. Moreover, none of Apotex's experts testified that the Lever patent anticipates the invention of the '805 patent.

2. Mast Cell Stabilization Is Not An Inherent Property of Olopatadine

337. The concentration of olopatadine in Patanol® is 1 mg/mL, or 0.1% w/v. (Docket # 173, Stipulation ¶ 10). At that concentration, it stabilizes the mast cells in the human eye. (Kaliner Tr. 683:15-23).

338. Not every concentration of olopatadine applied to the human eye will stabilize the mast cells in the human eye. (Kaliner Tr. 745:4-18 ("THE COURT: Well, it would just happen, wouldn't it, Doctor? I mean, if you're using it as an antihistamine, olopatadine, it's going to be a mast cell stabilizer in any event, right? THE WITNESS: # It would have to be at the right concentration and right . . . formulation.")). Dr. Kaliner testified, for example, that olopatadine at 0.001% would not stabilize human conjunctival mast cells. (Kaliner Tr. 756:23-757:1). Apotex's expert, Dr. Bielory, testified that not every concentration of olopatadine will work as a mast cell stabilizer. (Bielory Tr. 1164:7-1165:2 (agreeing that "not every concentration of olopatadine is going to effectively stabilize mast cells"; agreeing that you won't get "the clinical effect that you want" at every concentration of olopatadine)).

339. Compositions containing olopatadine at concentrations that do not stabilize conjunctival mast cells to a clinically relevant extent do not satisfy the limitation of claim 1 of the '805 patent (requiring stabilizing human conjunctival mast cells), and use of those concentrations would therefore not fall within any of the dependent claims of the '805 patent for the same reason. (Kaliner Tr. 757:2-4).

C. Inequitable Conduct

340. Apotex contends that Dr. Yanni and Mr. Ryan committed inequitable conduct during the prosecution of the '805 patent by selectively disclosing only favorable PARC test results and withholding the adverse Wellcome HCMC test results.

Apotex further contends that Dr. Yanni and Mr. Ryan committed inequitable conduct by making arguments in support of patentability that were directly contradicted by the Wellcome HCMC test results.

1. The Wellcome HCMC Test Results Were Not Material to Patentability

a. The Wellcome HCMC Data Was Inconclusive But Tended to Show that the Wellcome Compounds Were Biphasic

341. As noted above, the examiner rejected the Applicants' claims in both the '227 and '729 applications on grounds of obviousness in light of the Lever patents (which disclosed the Wellcome Compounds). Thus, to overcome the examiner's rejection, Alcon had to demonstrate that olopatadine was unexpectedly superior to the closest prior art compounds. *See In re Baxter Travenol Labs*, 952 F.2d 388, 392 (Fed. Cir. 1991) ("[W]hen unexpected results are used as evidence of nonobviousness, the results must be shown to be unexpected compared with the closest prior art.").

342. Alcon therefore performed three comparative tests of olopatadine, the E-isomer, and Wellcome Compounds I and II in an HCMC assay, and reported the results in the Kyowa Report. (TX 995; TX 244; *see also supra* Finding of Fact # 113).

343. Alcon chose those compounds because they were the closest prior art compounds to olopatadine. The E-isomer was encompassed by the genus disclosed in the Lever patents and was the closest prior art compound to olopatadine. (Ryan Tr. 1567:21-1568:1; Smith Tr. 1392:4-18; Bielory Tr. 1199:17-19). Wellcome

Compounds I and II were the closest compounds specifically taught in the Lever patents. (Bielory Tr. 1199:11-19).

344. The first test, conducted on February 17, 1994, compared Wellcome Compounds I and II to olopatadine. (TX 994; Yanni Tr. 241:15-242:4). Given the limited quantities of the Wellcome Compounds that he had, Dr. Yanni tested them within the range of $10^{-3.25}$ and $10^{-4.25}$ Molar concentrations. He used this range because he thought it could provide an answer regarding whether the compounds had no activity or potentially showed a stimulatory effect on the release of histamine. (Yanni Tr. 242:5-16).

345. Dr. Yanni believed the results of this experiment were inconclusive, although the beginning of a downward trend was consistent with the biphasic effect. (Yanni Tr. 242:20-243:8, 244:11-245:3; TX 995 at ALP013-118430). Because Dr. Yanni knew that the Wellcome Compounds were antihistamines, he believed that further testing would likely show that they were in fact biphasic. (Yanni Tr. 244:18-245:3).

346. Dr. Yanni thus conducted a second test on February 24, 1994, and compared the Wellcome Compounds and the E-isomer to olopatadine. (TX 244; Yanni Tr. 245:14-246:2). The data was consistent with Wellcome Compounds I and II being biphasic, but the data was incomplete because Dr. Yanni did not have enough of the compounds to test sufficiently high concentrations. (Yanni Tr. 246:9-249:9, 250:11-25; *see also* Abelson Tr. 1787:14-1788:10 ("[T]his study is incomplete,

and it must be looked at as inconclusive."); Kaliner Tr. 663:2-7).

347. Dr. Yanni then looked at the combined data, and concluded that the Wellcome Compounds were most likely biphasic because the left side of the curve trended upward, and the slope on the right side of the curve trended sharply downward, as one would expect with biphasic curves. (Yanni Tr. 246:9-249:9, 268:18-269:10; *see also supra* Finding of Fact # 115).

348. Dr. Yanni's conclusion was a "reasonable interpretation" of the curve, "consistent with what a person of skill[] in the art in 1995 would have made." (Kaliner Tr. 663:21-665:7, 758:17-24).

349. A reasonable examiner would not have wanted to know about incomplete and inconclusive data, and it would have been improper to submit incomplete and inconclusive data to him. (Killworth Tr. 1966:10-1967:9, 1973:4-12).

350. In addition, as noted earlier, biphasic compounds cannot be dosed to a patient at the point where they inhibit histamine release. (Yanni Tr. 173:5-16; *see also supra* Finding of Fact # 88). As a result, these compounds cannot be superior human conjunctival mast cell stabilizers as compared to olopatadine. (Yanni Tr. 173:5-16; Kaliner Tr. 527:3-528:16, 532:1-14; Abelson Tr. 1789:1-1790:2; Banker Tr. 943:11-15, 885:4-19, 921:24-922:23, 923:22-924:5, 927:10-17).

b. The Wellcome HCMC Data Was Not Inconsistent With Table 3 in the '729 Application

351. Table 3 of the '729 application is gleaned from Table 1 of the Kyowa Report.

(*Compare* TX 4 at ALP001-042014, *with* TX 794 at ALP001-002286; *see also supra* Finding of Fact # 123). Table 3 reflects that data comparing olopatadine with the Wellcome Compounds in the PARC assay. (TX 4 at ALP001-042014).

352. The '729 application describes the PARC assay, performed in the conjunctiva of a rat, as follows: "This assay indicates whether a topically applied compound effectively prevents or decreases the local allergic response in the conjunctiva. This assay allows an assessment of bioavailability following topical dosing." (TX 4 at ALP001-042014).

353. The claims of the '729 application as originally filed were not limited to humans or to mast cell stabilization. (TX 4 at ALP001-042022-25; Ryan Tr. 1597:7-23, 1602:2-5; Killworth Tr. 1984:1-1985:10).

354. As a result, the inclusion of the PARC test data in Table 3 showing superior anti-allergic activity would be sufficient to demonstrate unexpected properties and overcome a rejection of obviousness. (TX 762, Manual of Patent Examining Procedure ("MPEP") 716.02(a) ("Evidence that a compound is unexpectedly superior in one of a spectrum of common properties can be enough to rebut a *prima facie* case of obviousness. No set number of examples of superiority is required.") (quotations omitted); Killworth Tr. 1984:1-1986:1).

355. Although the MPEP requires examiners to consider test data in the specification, (Smith Tr. 1336:16-1337:4), there was no assertion in the specification that the comparative data that was included in Table 3 showed that olopatadine and the E

isomer were superior *human* conjunctival mast cell stabilizers to Wellcome Compounds I and II. (Killworth Tr. 2000:3-2002:4) (emphasis added).

c. The Wellcome HCMC Data Was Not Inconsistent With Table 3 in the October 1996 Amendment (the Paragraph (iv) Argument)

356. In paragraph (iv) of the October 1996 amendment to the '729 application (following the examiner's § 103 obviousness rejection), Mr. Ryan argued that even if one ignored his prior arguments in paragraph (ii) regarding the mast cell heterogeneity principle, there is "no way to predict, given the disclosures of Kamei et al. and Lever, that the compounds recited in Applicants' Claims would possess significantly superior conjunctival mast cell stabilization activity compared to the structurally similar compounds exemplified by Lever." (TX 4 at ALP001-042094). He then referred to Table 3 of the specification and explained that it "illustrates the statistically significant superior mast cell stabilization activity that the Z- and E- isomers of the 2-acetic acid derivative [olopatadine and the E isomer] have compared to the 2-carboxylic acid and 2-acrylic acid derivatives exemplified by Lever [Wellcome I and II]." (TX 4 at ALP001-042094).

357. Mr. Ryan was arguing that if for some reason one decided to ignore the mast cell heterogeneity principle and therefore assume that animal test results are equivalent to human test results, then the data showed that olopatadine was a superior human conjunctival mast cell stabilizer to Wellcome Compounds I and II. (Ryan Tr.

1613:2-11, 1615:3-24; Killworth Tr. 1989:7-22[6]; Smith Tr. 1380:20-1382:14).

358. Although Table 3 by itself does not demonstrate human conjunctival mast cell activity, it is reasonable to conclude from the data in the '729 application's specification as a whole, that olopatadine is a superior human conjunctival mast cell stabilizer as compared to Wellcome Compounds I and II. This is because the other data in the specification already shows that olopatadine is an effective human conjunctival mast cell stabilizer. Given this data, the POOS looking at Table 3, and ignoring mast cell heterogeneity, would conclude that the superior anti-allergic effect of olopatadine shown in Table 3 is a consequence of its superior human conjunctival mast cell stabilizing activity. (Kaliner Tr. 678:8-679:20; Yanni Tr. 315:8-317:4). Even Apotex's expert, Dr. Banker, reached the conclusion that Table 3 shows that olopatadine and the E isomer are superior human conjunctival mast cell stabilizers compared to Wellcome Compounds I and II in light of other data in the '729 application. (Banker Tr. 948:2-950:23 (references his deposition testimony which is part of the record)).

359. Subsequent testing further confirms that the argument in paragraph (iv) of the October 1996 amendment is true. In 2008, Mr. Miller, the Alcon scientist who co-developed the HCMC assay and has performed more than 200 tests using that assay, tested Wellcome Compounds I and II in the HCMC test. Mr. Miller's 2008

[6] This excerpt from the trial transcript erroneously uses the word "wouldn't" rather than "would" at 1989:11, as the surrounding context makes clear.

test was scientifically valid, using a number of controls and a reference standard. Mr. Miller did not know what the compounds were when he tested them or what results would be useful to Alcon in this litigation. (Miller Tr. 1510:5-1512:7. 1512:8-1525:1).

360. The 2008 tests show that Wellcome Compounds I and II exhibit a biphasic curve. They inhibited histamine release at 10^{-3} Molar and potentiated histamine release at 10^{-2} Molar. (TX 206; Kaliner Tr. 669:20-670:7; Miller Tr. 1512:8-1525:1; Abelson Tr. 1788:19-20, 1789:2-13).

361. The 2008 testing conclusively demonstrates that olopatadine is a superior human conjunctival mast cell stabilizer as compared to Wellcome Compounds I and II (which are not mast cell stabilizers given their biphasic nature); accordingly, the statement in paragraph (iv) was true. (Kaliner Tr. 750:10-15; Abelson Tr. 1788:16-1790:2; Killworth Tr. 1989:23-1990:9).

d. The Examiner Could Not Have Relied on Paragraph (iv) in Allowing the '729 Application

362. On November 14, 1996, the examiner issued a Notice of Allowability indicating that claims 1-12 were allowed. (TX 4 at ALP001-042095; Ryan Tr. 1623:20-1624:13).

363. MPEP 716.01(c) requires that attorney argument about unexpected results (such as the argument in paragraph (iv) of the October 1996 amendment) cannot take the place of evidence. Assertions regarding unexpected results must be supported by

an appropriate affidavit or declaration. (TX 762; Killworth Tr. 2017:5-17).

364. Although the data in Table 3 of the specification was supported by the declaration that the inventors signed when they filed the application, (Smith Tr.1336:8-15), the arguments about what the data showed were not supported by a declaration as the MPEP requires. (TX 762 at 700-143 (MPEP § 716.01(c)); Killworth Tr. 2017:5-2018:9). The examiner would have asked for a declaration if he sought to rely on paragraph (iv). He did not ask for one; thus, the court reasonably concludes that the examiner did not rely on that argument. (Killworth Tr. 2018:10-2019:12).

2. Dr. Yanni and Mr. Ryan Did Not Deliberately Withhold the Wellcome HCMC Data in the Kyowa Report With Deceptive Intent

a. Dr. Yanni and Mr. Ryan Reasonably Believed that the Results Reflected that Olopatadine Was Superior to Wellcome Compounds I and II

365. Dr. Yanni, as one of the inventors of the ‘805 patent, and Mr. Ryan, as the attorney responsible for prosecuting the ‘227 and ‘729 applications (which issued as the ‘805 patent), had a duty of candor to the PTO. 37 C.F.R. § 1.56(c) (providing that the duty of candor extends to “each inventor named in the application; each attorney or agent who prepares or prosecutes the application; and every other person who is substantively involved in the preparation or prosecution of the application and who is associated with the inventor, with the assignee or with anyone to whom there is an obligation to assign the application.”). Apotex contends that Dr. Yanni and Mr. Ryan violated this duty by deliberately

withholding the Kyowa Report – more particularly, the HCMC data – with deceptive intent.

366. As noted previously, Dr. Yanni conducted two HCMC tests of the Wellcome Compounds and olopatadine in February of 1994 in an effort to overcome the patent examiner's obviousness rejection. (*See supra* Findings of Fact ## 344, 346).

367. Dr. Yanni regarded the 1994 testing as very favorable as it related to the comparison of olopatadine to Wellcome Compounds I and II. The PARC tests showed that both olopatadine and the E isomer were significantly more active than Wellcome Compounds I and II. (Yanni Tr. 279:21-280:20). Although the HCMC tests were inconclusive as to Wellcome Compounds I and II, Dr. Yanni believed that the curves were consistent with those of biphasic compounds he had tested in the past. (Yanni Tr. 246:9-249:9, 268:18-269:10; *see also supra* Finding of Fact # 115).

368. Mr. Ryan understood the 1994 testing showed that olopatadine was superior to Wellcome Compounds I and II, but similar to the E isomer. (Ryan Tr. 1569:11-1570:5).

369. Dr. Yanni's and Mr. Ryan's beliefs about the 1994 testing are consistent with the contemporaneous documents. On April 14, 1994, Dr. Robert Adamski ("Dr. Adamski"), a member of Alcon's business licensing group, (Yanni Tr. 205:3-13; Ryan Tr. 1574:2-11), sent Kyowa a letter attaching the 1994 Report, stating that

"[f]rom the report you'll see a significant difference in activity between olopatadine and the two Wellcome compounds, while the E isomer of olopatadine approximated the activity seen with the parent compound." (TX 442; Yanni Tr. 308:23-309:20; Ryan Tr. 1585:25-1587:22). Prior to sending this letter to Kyowa, Dr. Adamski spoke with Dr. Yanni and Dr. Yanni relayed to Dr. Adamski his beliefs as to what the data showed. (Yanni Tr. 303:21-304:6).

370. In a responsive letter, Kyowa also recognized that the test data comparing Wellcome Compounds I and II to olopatadine had been favorable, stating "[w]e are glad to hear that KW4679 is more active than Wellcome Compounds in your experiment." (TX 774). That was consistent with Dr. Yanni's and Mr. Ryan's understanding of the data. (Ryan Tr. 1574:2-24; Yanni Tr. 303:21-305:9, 308:23-310:9).

371. Additional evidence supporting Dr. Yanni's intent is the fact that he checked "no further interest" in the compound status reports for Wellcome Compounds I and II following the test results. (TX 419 at ALP013-113813-14; *see also supra* Finding of Fact # 117).

b. Dr. Yanni and Mr. Ryan Did Not Selectively Disclose Only Favorable Test Results and Withhold Adverse Test Results With Deceptive Intent

372. When Mr. Ryan drafted the CIP application, he received a copy of the Kyowa Report from Dr. Yanni. (TX 794; Ryan Tr. 1650:9-11). The copy of the document had circles around the description of the PARC test protocol and the

data for the PARC test, reflected on the Kyowa Report at Table 1. (TX 794). Dr. Yanni decided what information in the 1994 test was relevant, and the circles reflect the information that Dr. Yanni believed was relevant in the report. (Yanni Tr. 294:11-20, 331:17-332:11; Ryan Tr. 1582:6-12).

373. The circled information, including the description of the PARC test data, was incorporated into the draft CIP application. Table 1 from the Kyowa Report was submitted as Table 3 in the draft CIP. (*Compare* TX 794 at ALP001-002285, *with* TX 2069 at ALP001-002355-56; *see also supra* Finding of Fact # 123).

374. Mr. Ryan only reviewed those portions of the Kyowa Report (Exhibit 794) that he was directed to for the purpose of preparing the CIP. (Ryan Tr. 1582:13-1585:8). Mr. Ryan did not have the expertise on his own to independently analyze or understand the data in the report. (Ryan Tr. 1582:13-1585:8) ("THE COURT: And your testimony is you were directed by Dr. Yanni? THE WITNESS: Yes, that's right, Your Honor. I just know – I know that this technical report, I wouldn't have decided which portions of it I would use myself or which portions had any specific meaning. THE COURT: Do you have the expertise to do that? THE WITNESS: No, sir."), 1553:25-1554:7 (Mr. Ryan is not a person of ordinary skill in the art; rather, he has a bachelor's degree in chemical engineering and a law degree)).

375. The same PARC discussion and data (Table 3) was likewise submitted in the '729 application, which eventually issued as the '805 patent. (TX 4; *see also*

supra Finding of Fact # 132).

376. Mr. Ryan did not go back to look at the Kyowa Report in the Summer of 1995 when he prepared the '729 application or at anytime thereafter. (Ryan Tr. 1601:18-22, 1621:19-23). A copy of the Kyowa Report was not found in his file for the '805 patent; it was found in his file for the abandoned '227 application. (Ryan Tr. 1576:22-1577:10). He did not return to his '227 application file in 1995 or 1996. (Ryan Tr. 1596:10-17, 1617:10-23).

377. There is no reason to think that Mr. Ryan remembered the Kyowa Report, much less Figure 1 reflecting the HCMC data, more than a year later when he filed the '729 application in the Summer of 1995, or more than two years later when preparing the October 1996 amendment. (Smith Tr. 1380:10-13 (acknowledging that people who are preparing patent applications may see something and forget about it even just a few weeks later)).

378. Mr. Ryan did not make a deliberate decision to withhold Figure 1 (the HCMC data) of the Kyowa Report with intent to deceive the PTO at any point in time. (Ryan Tr. 1618:7-1619:4, 1601:20-25).

379. Dr. Yanni did not selectively disclose only the PARC test data while withholding the HCMC data. (Yanni Tr. 331:17-332:11). Rather, as noted above, he believed that the PARC test data was very favorable, and that the HCMC test data was inconclusive. (Yanni Tr. 331:24-332:3; *see also supra* Finding of Fact # 115). He therefore concluded that the data was not relevant to the issue of unexpected

properties of olopatadine compared to the Wellcome Compounds I and II. (Yanni Tr. 332:4-19).

380. The court finds the testimony of Dr. Yanni and Mr. Ryan to be highly credible.

c. The Totality of the Circumstances Do Not Warrant A Finding of Deceptive Intent

381. Apotex's final argument is that the "totality of the facts and circumstances" permits an inference of Plaintiffs' deceptive intent with respect to the Kyowa Report. The totality of the circumstances cited by Apotex in support of this theory includes the following alleged misrepresentations or omissions: (1) Mr. Ryan's failure to disclose the rejection of the '227 application in the '729 application; and (2) Dr. Yanni's and Mr. Ryan's repeated failure to include the Wellcome HCMC test data in those applications. Apotex also argues that Alcon advanced at trial "litigation-inspired" theories, including: (1) Dr. Yanni's explanation for the omitted sentence in the Kyowa Report; and (2) Dr. Yanni's assertion that he believed the Wellcome Compounds were biphasic in light of the information contained in his 2007 patent application. These, too, are addressed below.

(1) Mr. Ryan's Failure to Disclose the '227 Application Is Not Evidence of An Intent to Deceive

382. Mr. Ryan did not disclose to the PTO the fact of the abandoned '227 application or the rejection from that application. (Ryan Tr. 1603:19-1604:14).

383. The abandoned patent application is not prior art and could not have been the basis for a rejection. (Ryan Tr. 1603:19-1604:7; Killworth Tr. 1958:8-20; Smith Tr.

1390:11-23).

384. As of 1995, the Federal Circuit had never held that there was an obligation to disclose a prior abandoned application or a rejection in a prior patent application. (Smith Tr. 1390:2-5; Killworth Tr. 1960:8-10, 1961:5-9).

385. It was not routine practice to patent practitioners in the mid-1990s to disclose rejections in earlier related prosecutions; instead, they would make sure that all of the same prior art was brought to the examiner's attention, as Mr. Ryan did here. (Killworth Tr. 1961:10-18).

386. The fact that the '227 application was abandoned was not material to the prosecution of the '805 patent, and the failure to disclose it to the PTO is not evidence of an intent to deceive.

(2) The Repeated Failure to Disclose the Wellcome HCMC Test Data Is Not Evidence of Deceptive Intent

387. The Wellcome HCMC test data was not disclosed in the '227 or '729 applications.

388. The Wellcome HCMC test data was not material to the prosecution of the '805 patent. (*See supra* Findings of Fact § VI.C.1).

389. Dr. Yanni and Mr. Ryan did not withhold the Wellcome HCMC test data with an intent to deceive. (*See supra* Findings of Fact § VI.C.2).

390. The "repeated" failure to disclose the Wellcome HCMC test data is not evidence of an intent to deceive.

(3) The Sentence Deleted From the Kyowa Report Did Not Reflect that Wellcome Compounds I and II Were Superior Mast Cell Stabilizers Than Olopatadine and Is Not Evidence that Dr. Yanni and Mr. Ryan Exhibited an Intent to Deceive

391. The Summary Section of the Kyowa Report reads:

> The Kyowa Hakko-supplied Wellcome compounds I and II and the (E)-isomer of KW-4679 were evaluated following topical ocular administration in an animal model of allergic conjunctivitis. At 0.1%, each of the three compounds significantly inhibited the passive anaphylactic response in rat conjunctiva when applied to the eye 20 minutes prior to antigen challenge.
>
> In vitro, Wellcome compounds I and II ($10^{-3.5}$ - $10^{-5.5}$ M) and the KW-4679 (E)-isomer ($10^{-3.5}$ M) inhibited the release of histamine from human conjunctival mast cells stimulated with anti-human IgE.
>
> *These data do not provide a basis for circumventing the Wellcome patent covering the anti-allergic utility of KW-4679 and related compounds.*

(TX 794) (emphasis added).

392. The italicized sentence did not appear in the copy of the report that was sent to Kyowa or in the version that was sent to the Alcon archives. (Yanni Tr. 322:19-326:20). Dr. Yanni did not remove that sentence and does not know how it was removed. (Yanni Tr. 326:11-17).

393. This statement reflects the fact that the data did not support an assertion that olopatadine was superior to the E isomer, which was within the scope of the Lever patent. (Yanni Tr. 286:3-20).

394. It further reflects Dr. Yanni's concern that Kyowa had not yet obtained a license from Burroughs Wellcome, even to olopatadine, by 1994. (Yanni Tr. 286:3-20). By that time, Alcon had a license from Kyowa to the olopatadine compound but Kyowa did not have a license from Burroughs Wellcome for olopatadine or the E isomer, which were encompassed by the Lever patents. (TX 24; Ryan Tr. 1571:9-24; Yanni Tr. 224:2-9).

395. The inclusion of this sentence in one internal version of the Kyowa Report does not reflect deceptive intent.

(4) Dr. Yanni's 2007 Patent Application Does Not Refute His Belief that the Wellcome Compounds Were Biphasic

396. Dr. Yanni is a named inventor on United States Patent Application # 11/947,041 (the '041 application"), entitled "Use of Connective Tissue Mast Cell Stabilizers to Facilitate Ocular Surface Re-Epithelization and Wound Repair." (TX 524). The '041 patent application was filed on November 29, 2007 and published on June 12, 2008. (TX 524 at AI009824).

397. Dr. Yanni testified that the invention relates primarily to preventing the release of chymase from cells as a way of healing ophthalmic or dermal – i.e., eye and skin – wounds. (Yanni Tr. 327:6-328:4).

398. One of the embodiments of the invention claimed in the '041 patent application is a conjunctival wound. A conjunctival wound may include a conjunctival disease, such as allergic conjunctivitis. (TX 524 at AI009826).

399. Wellcome Compounds I and II are on a list of compounds that are identified by chemical name as potential mast cell stabilizers in that application, a list that stretches a full four columns through the patent. (TX 524 at AI009826-28). The '041 patent application does not state that they are human conjunctival mast cell stabilizers, and in fact the invention, as noted above, is explicitly related to treating ophthalmic or dermal wounds. (TX 524; Yanni Tr. 328:5-14, 435:4-17).

400. Dr. Yanni did not draft this patent application, although he did review it quickly before signing it. (Yanni Tr. 330:6-10). He would not have been able to discern the identity of each individual compound listed from the long list of compounds listed in the application. (Yanni Tr. 330:11-22).

401. Dr. Yanni did not notice or recognize when he reviewed the application whether any of the listed compounds were from the Lever patents, or notice that the Lever patents were identified by patent number. (Yanni Tr. 330:23-331:15). The Lever patents were never identified by named inventor or assignee anywhere in the application. (TX 524).

402. Mr. Ryan did not draft the patent application. An outside law firm drafted it and several other applications because Alcon's patent department had a backlog of applications to be drafted. (Ryan Tr. 1631:12-1632:3; Yanni Tr. 328:22-329:12). Mr. Ryan did the ministerial act of filing the application that outside counsel had prepared in order to try to save money. (Ryan Tr. 1632:4-15).

403. Prior to filing the application, Mr. Ryan did not remember noticing that the Lever

patents were listed in the application by patent number, and did not recognize the individual compounds from Lever listed in the application. (Ryan Tr. 1633:2-20 (testifying that he "wouldn't have done anything more than recognize that there was a long list of chemical names, and I would have skipped past that part and kept skimming to make sure that the parts looked like they fit together, that it had a complete set of claims, that the application looked like it was ready to file, and I would have sent it in.")).

D. Written Description

404. The court construed the term "stabilizing conjunctival mast cells" in claim 1 of the '805 patent to mean "preventing or reducing release of mediators including histamine from mast cells in the conjunctiva *to an extent clinically relevant in the treatment of allergic eye disease*." (Docket # 282, Order on Claim Construction).

405. Apotex contends that the '805 patent fails for lack of a written description under 35 U.S.C. § 112 because it does not contain any clinical data or testing in a living human being, as required by the court's claim construction. This theory was not raised pre-trial. (Docket # 317, Alcon's Proposed Findings of Fact, Exs. D and E).

406. The PTO examiner of the '805 patent allowed the claims without requesting clinical data or issuing a rejection for an insufficient written description. (TX 4).

407. The '805 patent reasonably conveys to those skilled in the art that the inventors were in possession of the claims' subject matter as of the filing date.

408. In particular, the specification of the '805 patent reasonably conveys to those

skilled in the art that the inventors were in possession of the invention of claim 1 of the '805 patent – *i.e.*, a method for treating allergic eye diseases in humans comprising "preventing or reducing release of mediators, including histamine, from mast cells in the conjunctiva to an extent clinically relevant in the treatment of allergic eye disease." The '805 patent is explicit from the beginning that the invention relates to the use of olopatadine or the E isomer for treating and/or preventing allergic eye disease. (TX 3A, Abstract, col. 1, ll. 7-14).

409. The patent also discusses mechanisms of action, referring to mast cell stabilization in the first two columns of the patent. (*See* TX 3A, col. 1 – col. 2). For example, the specification discusses at length the fact that certain compounds stabilize mast cells in animals but not humans, and that the invention is directed to a mast cell stabilizer that is effective in stabilizing the mast cells in the human conjunctiva for the treatment of allergic eye disease. (TX 3A, col. 1, l. 43 – col. 3, l. 23). Treating or preventing allergic eye disease through mast cell stabilization necessarily means that there must be clinically relevant effects at least in part through mast cell stabilization.

410. The specification makes explicit reference to the clinical context, stating: "Topical ophthalmic formulations which contain drugs having conjunctival mast cell activity may only need to be applied once every 12-24 hours instead of once every 2-4 hours. One disadvantage to the ophthalmic use of reported anti-allergic drugs which in fact have no human conjunctival mast cell stabilizing activity is an

increased dosage frequency." (TX 3A, col. 2, ll. 20-26). This sentence reasonably conveys that the context of the '805 patent invention was one of a clinically useful invention, as it expressly discusses the dosing regimen that can be used with an effective human conjunctival mast cell stabilizer. This description is further confirmed by the statement that "[w]hat is needed are topically administrable drug compounds which have demonstrated stabilizing activity on mast cells obtained from human conjunctiva . . . ." (TX 3A, col. 2, ll. 56-61).

411. The specification states that "Compound A [i.e., olopatadine and/or the E isomer] has human conjunctival mast cell stabilizing activity . . . ." (TX 3A, col. 3, ll. 18-24). In the context of the specification which discusses a product for clinical use and even provides pharmaceutical formulations of the product, the person of ordinary skill would understand this statement to refer to the fact that olopatadine can be used to achieve a clinically relevant amount of mast cell stabilization.

412. The '805 patent goes on to describe at length the *in vitro* HCMC assay for testing human conjunctival mast cell stabilizing effect. (TX 3A, col. 3, l. 43 – col. 5, l. 23). As of June 1995, this assay was the best and only way of assessing human conjunctival mast cell activity outside of a clinical trial. (Yanni Tr. 165:16-167:15; Kaliner Tr. 524:2-7). Table 1 of the patent, entitled "Compound Effect on Histamine Release from Human Conjunctival Tissue Mast Cells upon anti-Human IgE Challenge" reports the results of performing this test on olopatadine as well as two known compounds – cromolyn and nedocromil. The patent states that "[a]s

Table 1 clearly shows, the anti-allergic drugs disodium cromoglycate and nedocromil failed to significantly inhibit human conjunctival mast cell degranulation. In contrast, Compound A (cis isomer) produced concentration-dependent inhibition of mast cell degranulation," TX 3A, col. 4, ll. 41-45. In the context of the patent's repeated description of olopatadine's usefulness to treat allergic eye disease through mast cell stabilization, Table 1 clearly describes stabilizing mast cells to an extent clinically relevant in the treatment of allergic eye disease.

413. The discussion of Table 1 unequivocally describes the concept of achieving clinically relevant mast cell stabilization. As explained in Plaintiffs' *Markman* papers and at oral argument, the patent distinguishes between the minimal inhibition of cromolyn and nedocromil, which it does not characterize as mast cell stabilization, with the significant inhibition of olopatadine that it does characterize as mast cell stabilization. (*See* TX 3A, col. 4, l. 41 – col. 5, l. 23).

414. The '805 patent specification also specifically describes a 0.1% olopatadine eye drop formulation, TX 3A, col. 7, ll. 1-15, and, as explained in Findings of Fact Section VI.A.5, the testimony of record establishes that such a 0.1% eye drop will, in fact, stabilize human conjunctival mast cells to a clinically relevant degree.

415. Dr. Kaliner, in his Claim Construction Report, agreed that the invention of the '805 patent described a clinically relevant extent of mast cell stabilization. The court finds that if Dr. Kaliner had the opportunity to testify on this issue at trial, his

testimony would have been the same as in his Claim Construction Report:

a. "The '805 patent describes a method of treating allergic eye disease in humans through stabilizing conjunctival mast cells using a therapeutically effective amount of olopatadine. The whole point of the method described is to stabilize human conjunctival mast cells and be therapeutically effective in addressing the signs and symptoms of allergic eye disease." (*See* Docket # 243, Plaintiffs' Opening Claim Construction Brief, Ex. 1B, ¶ 58).

b. "Apotex's proposed definition, which defines 'stabilizing conjunctival mast cells' as including any inhibition in the release of mediators, would include minor amounts of stabilization of mast cells, even those that had no relevant effect on the treatment of a patient's allergic eye disease. That is not what the person of ordinary skill would understand this term to mean in the context of the '805 patent." (*See* Docket # 243, Plaintiffs' Opening Claim Construction Brief, Ex. 1B, ¶ 59).

c. "The entire point of the discussion in the specification and the file history however is that [nedocromil and cromolyn] are not [mast cell stabilizers], and that a compound that can effectively stabilize human conjunctival mast cells prevents or reduces release of mediators to an extent clinically relevant in the treatment of allergic eye disease, is needed." (*See* Docket # 243, Plaintiffs' Opening Claim Construction Brief, Ex. 1B, ¶ 56).

416. A clinically relevant extent of mast cell stabilization is described in the '805 patent

specification. It is for that same reason that Alcon advanced their claim construction position requiring a clinically relevant mast cell stabilization in the first place; it was the construction that most naturally aligned with specification. The court adopted this claim construction. There is no clear and convincing evidence that the specification does not describe the claim limitation at issue to the person of ordinary skill in the art.

CONCLUSIONS OF LAW

1. To the extent any of the foregoing findings of fact is a conclusion of law, it is hereby adopted as a conclusion of law. To the extent any of the conclusions of law set forth below is a finding of fact, it is hereby adopted as a finding of fact.

I. Controlling Authority

A. Jurisdiction

2. The court has subject matter jurisdiction over this case pursuant to 28 U.S.C. §§ 1331 and 1338(a).

3. The 1984 Hatch-Waxman amendments to the Federal Food, Drug, and Cosmetic Act regulate the process by which generic drug companies gain approval from the FDA to bring generic pharmaceuticals to market. 21 U.S.C. § 355.

4. Under 35 U.S.C. § 271(e)(2)(A), the filing of an ANDA with the FDA containing a "Paragraph IV" certification as to a given patent constitutes an act of infringement of that patent. *Janssen Pharmaceutica, N.V. v. Apotex, Inc.*, 540 F.3d 1353, 1356 (Fed. Cir. 2008) ("In order to bring about early resolution of patent disputes between generics and pioneering drug companies, the [Hatch-Waxman] Act provides that the filing of a Paragraph IV Certification is an act of patent infringement.").

5. Because litigation arising from the filing of a Paragraph IV Certification involves circumstances where the alleged infringer has not yet commercially manufactured or sold its ANDA product, "section 271(e)(2)(A) makes it possible for a patent

owner to have the court determine whether, if a particular drug *were* put on the market, it *would* infringe the relevant patent." *Bristol-Myers Squibb Co. v. Royce Labs., Inc.*, 69 F.3d 1130, 1135 (Fed. Cir. 1995) (emphasis in original). "If the court determines that the [challenged] patent is not invalid and that infringement *would* occur, and that therefore the ANDA applicant's paragraph IV certification is incorrect, the patent owner is entitled to an order that FDA approval of the ANDA containing the paragraph IV certification not be effective until the patent expires." *Id*.

B. Federal Circuit Law Applies

6. Any appeal in this action, which arises under the patent laws of the United States, must be to the United States Court of Appeals for the Federal Circuit, 28 U.S.C. § 1295(a), whose precedent governs matters of substantive patent law in this court. The Federal Circuit has adopted decisions of the Court of Customs and Patent Appeals ("C.C.P.A.") as its own precedent, making those decisions binding on this court. *E.g.*, *Southwire Co. v. Essex Group, Inc.*, 220 U.S.P.Q. 1053, 1056 n.6 (N.D. Ill. 1983) ("The law that controls this action . . . is the law of the Federal Circuit [, which] has declared that the patent decisions of [the C.C.P.A.] will be considered binding . . . .") (citing *South Corp. v. United States*, 690 F.2d 1368, 1370 (Fed. Cir. 1982) (en banc)).

II. Infringement of the '805 Patent

7. Plaintiffs have the burden of proving infringement by a preponderance of the

evidence. *Boehringer Ingelheim Vetmedica, Inc. v. Schering-Plough Corp.*, 320 F.3d 1339, 1353 (Fed. Cir. 2003).

8. "[A] district court's inquiry in a suit brought under § 271(e)(2) is the same as it is in any other infringement suit, *viz.*, whether the patent in question is invalid or *will not be infringed* by the manufacture, use or sale of the drug for which the [ANDA] is submitted." *Glaxo, Inc. v. Novopharm, Ltd.*, 110 F.3d 1562, 1569 (Fed. Cir. 1997) (brackets in original) (quotations omitted).

9. Because "the allegedly infringing drug has not yet been marketed . . . the question of infringement must focus on what the ANDA applicant will likely market if its application is approved, an act that has not yet occurred." *Id.* Thus, "[u]nder § 271(e)(2)(A), a court must determine whether, if the drug were approved based upon the ANDA, the manufacture, use, or sale of that drug would infringe the patent in the conventional sense." *Id.*

10. The infringement inquiry is a two-part process: the first step is to construe the claims, and the second step is to compare the accused product to the construed claims and determine whether each element recited by a claim is present in the accused product. *Elbex Video, Ltd. v. Sensormatic Elecs. Corp.*, 508 F.3d 1366, 1370 (Fed. Cir. 2007); *Monsanto Co. v. Parr*, 545 F.Supp.2d 836, 841 (N.D. Ind. 2008).

11. The court has construed two phrases from claim 1 of the '805 patent. The court construed the phrase "stabilizing conjunctival mast cells" to mean "[p]reventing or

reducing release of mediators including histamine from mast cells in the conjunctiva to an extent clinically relevant in the treatment of allergic eye disease." The court construed the phrase "therapeutically effective amount" to mean "[a]n amount of olopatadine that provides a clinically relevant reduction and/or prevention of the signs and/or symptoms of allergic eye disease after topical administration of the human eye." (Docket # 282, Order on Claim Construction).

12. Determining whether a patent's properly construed claims read on the accused product or process is a factual question, making a district court's determination of infringement a question of fact. *Intervet Am., Inc. v. Kee-Vet Labs., Inc.*, 887 F.2d 1050, 1053 (Fed. Cir. 1989).

13. Infringement requires the patentee to show that the manufacture, use, sale, offer for sale, and/or importation of the accused product meets each limitation of the asserted claims. *Baxter Healthcare Corp. v. Spectramed, Inc.*, 49 F.3d 1575, 1582 (Fed. Cir. 1995); *see AstraZeneca LP v. Apotex, Inc.*, 623 F.Supp.2d 579, 598 (D.N.J. 2009) ("In order to prove infringement, the plaintiff must show that the accused product or method includes every limitation of an asserted claim of a patent.").

14. Courts routinely rely upon the proposed labeling and package inserts provided in an ANDA to support a finding of infringement, whether the infringement is direct, induced, or contributory. *Wyeth v. Sandoz, Inc.*, 703 F.Supp.2d 508, 516, 521 (E.D.N.C. 2010); *Eli Lilly & Co. v. Actavis Elizabeth LLC*, 676 F.Supp.2d 352,

377-78 (D.N.J. 2009); *AstraZeneca*, 623 F.Supp.2d at 598-99; *In re Omeprazole Patent Litig.*, 490 F.Supp.2d 381, 499 (S.D.N.Y. 2007); *Depomed, Inc. v. Ivax Corp.*, 532 F.Supp.2d 1170, 1181-82 (N.D. Cal. 2007); *Purdue Pharma L.P. v. Boehringer Ingelheim GmbH*, 98 F.Supp.2d 362, 377-78 (S.D.N.Y. 2000); *Ranbaxy Labs. Ltd. v. Abbott Labs.*, 2005 WL 3050608, at *23 (N.D. Ill. Nov. 10, 2005).

A. Direct Infringement

1. Apotex's ANDA Product Infringes Claim 1 of the '805 Patent, the Independent Claim

15. Apotex stipulated at trial that its ANDA product meets all but two of claim 1's limitations: (1) that its ANDA product stabilizes conjunctival mast cells to a clinically relevant extent; and (2) that its ANDA product is therapeutically effective in treating the signs and symptoms of allergic conjunctivitis. (*See* Kaliner Tr. 559:11-19, 560:5-10, 563:4-7, 564:2-5, 568:1-4; *see also* TX 131). In Apotex's Findings of Fact and Conclusions of Law, it contests only the first limitation; namely, that its ANDA product stabilizes conjunctival mast cells to a clinically relevant extent.

16. Patanol® prevents the release of mediators including histamine from mast cells in the conjunctiva to an extent clinically relevant in the treatment of allergic eye disease. (Kaliner Tr. 563:11-19) ("[A] huge body of information published in peer-reviewed literature . . . demonstrates that [Patanol®] inhibits mast cell

degranulation, and does so in a clinically effective way in humans in the eye.").

17. Patanol® treats all signs and symptoms of allergic conjunctivitis, including those that are "not typically effective or particularly attenuated or blocked with antihistamines," (Yanni Tr. 213:6-15), such as swelling, irritation, tearing, and redness. (Kaliner Tr. 541:12-543:10). Patanol®'s ability to block the additional signs and symptoms of allergic eye disease demonstrates its ability to inhibit the release of mediators from mast cells in the conjunctiva to a clinically relevant extent. (Yanni Tr. 210:15-19, 213:6-15; Kaliner Tr. 541:12-543:10).

18. Apotex's ANDA product "is the same product as Patanol®." (Kaliner Tr. 561:15-18). Apotex's ANDA product contains the same active and inactive ingredients in the same concentration as Patanol®, will be used for the same use as Patanol®, and administered in the same way and at the same dosage level as Patanol®. (*See supra* Findings of Fact ## 152-54).

19. Like Patanol®, Apotex's ANDA product will stabilize human conjunctival mast cells to a clinically relevant extent. (*See supra* Finding of Fact # 155).

20. Apotex presented no evidence to show that its ANDA product would not stabilize human conjunctival mast cells to a clinically relevant extent.

21. The court finds that Alcon has proven, by a preponderance of the evidence, that the use of Apotex's ANDA product would directly infringe claim 1 of the '805 patent.

2. Apotex's ANDA Product Infringes Claims 2-8 of the '805 Patent

22. In addition to meeting all the elements of claim 1, use of Apotex's ANDA product

also meets every limitation of dependent claims 2 through 8 of the ‘805 patent.

23. Claims 2-4 add the limitation that the composition be a solution and also provide particular concentration ranges for the amount of olopatadine. 0.1% w/v olopatadine falls within all of these ranges. (TX 3A; *see also* Findings of Fact # 145).

24. Claims 5-8 add to claim 1 that the compound used must be olopatadine, i.e., the Z isomer substantially free of the E isomer, and claims 6-8 provide particular concentration ranges for the amount of olopatadine. 0.1% w/v olopatadine falls within all of these ranges. (TX 3A; *see also* Findings of Fact ## 146-47).

25. Apotex stipulated at trial that its ANDA product is a solution containing 0.1% w/v olopatadine and that its ANDA product contains 0.1% olopatadine, the Z isomer, substantially free of the E isomer. (*See supra* Finding of Fact # 157).

26. The court finds that Alcon has proven, by a preponderance of the evidence, that the use of Apotex’s ANDA product would directly infringe claims 2-8 of the ‘805 patent.

B. Contributory Infringement

27. Pursuant to 35 U.S.C. § 271(c), “[w]hoever offers to sell or sells within the United States . . . a component of a patented machine, manufacture, combination or composition, or a material or apparatus for use in practicing a patented process, constituting a material part of the invention, knowing the same to be especially made or especially adapted for use in an infringement of such patent, and not a

staple article or commodity of commerce suitable for substantial noninfringing use, shall be liable as a contributory infringer."

28. Claims of contributory infringement may be brought as part of an ANDA infringement action under 35 U.S.C. § 271(e)(2). *Cf. Allergan, Inc. v. Alcon Labs., Inc.*, 324 F.3d 1322, 1330-32 (Fed. Cir. 2003). "The only difference in the analysis of a traditional infringement claim and a claim of infringement under section 271(e)(2) is the time frame under which the elements of infringement are considered." *Id*. at 1331.

29. Direct infringement is a prerequisite to a finding of contributory infringement. *Joy Techs., Inc. v. Flakt, Inc*., 6 F.3d 770, 774 (Fed. Cir. 1993) (citations omitted); *see also Aro Mfg. Co. v. Convertible Top Replacement Co.*, 365 U.S. 336, 341 (1961) ("[I]f there is no *direct* infringement of a patent there can be no *contributory* infringement.") (emphasis in original)).

30. Apotex's only argument is that Alcon has not proven, by a preponderance of the evidence, that Apotex's ANDA product directly infringes the '805 patent. As this issue has been decided in Alcon's favor, the court also finds that Alcon has proven, by a preponderance of the evidence, that Apotex will contribute to infringement of claims 1-8 of the '805 patent through the sale of its ANDA product.

31. Having found direct and contributory infringement, the court need not address the issue of whether Apotex is liable for inducing infringement.

III. The Validity of the '382 Patent

A. The Presumption of Validity

32. Patents are presumed valid. Each claim within a patent is independently presumed valid, even if other claims within the patent are held invalid. 35 U.S.C. § 282.

33. The burden of proving invalidity rests on the patent challenger, who must do so by clear and convincing evidence. 35 U.S.C. § 282; *Schumer v. Lab. Computer Sys., Inc*., 308 F.3d 1304, 1315 (Fed. Cir. 2002).

34. "The clear and convincing standard of proof of facts is an intermediate standard which lies somewhere between beyond a reasonable doubt and a preponderance of the evidence" and "has been described as evidence which produces in the mind of the trier of fact an abiding conviction that the truth of [the] factual contentions are 'highly probable.'" *Buildex Inc. v. Kason Indus., Inc.*, 849 F.2d 1461, 1463 (Fed. Cir. 1988) (internal quotations and citations omitted).

35. The burden "is constant and remains throughout the suit on the challenger" and "does not shift at any time to the patent owner." *TP Labs., Inc. v. Prof'l Positioners, Inc.*, 724 F.2d 965, 971 (Fed. Cir. 1984).

36. If a patent challenger alleges invalidity based on the prior art the PTO considered during prosecution of the patent, that challenger has the

> added burden of overcoming the deference that is due to a qualified government agency presumed to have properly done its job, which includes one or more examiners who are assumed to have some expertise in interpreting the references and to be familiar from their work with the level of skill in the

art and whose duty it is to issue only valid patents.

Ultra-Tex Surfaces, Inc. v. Hill Bros. Chem. Co., 204 F.3d 1360, 1367 (Fed. Cir. 2000) (quoting *Am. Hoist & Derrick Co. v. Sowa & Sons, Inc.*, 725 F.2d 1350, 1359 (Fed. Cir. 1984)). In other words, "the challenger's 'burden is especially difficult when the prior art was before the PTO examiner during prosecution of the application.'" *Al-Site Corp. v. VSI Int'l, Inc*., 174 F.3d 1308, 1323 (Fed. Cir. 1999) (quoting *Hewlett-Packard Co. v. Bausch & Lomb Inc*., 909 F.2d 1464, 1467 (Fed. Cir. 1990)).

B. Obviousness

37. The non-obviousness requirement is set forth in 35 U.S.C. § 103(a), and reads:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

38. Obviousness is a conclusion of law based on the following factual determinations: (1) the scope and content of the prior art, (2) the differences between the prior art and the claimed subject matter as a whole, (3) the level of skill in the art, and (4) where relevant, objective evidence of non-obviousness, i.e., the secondary considerations. *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966); *see also KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007); *Rolls-Royce, PLC v. United*

Tech. Corp., 603 F.3d 1325, 1338 (Fed. Cir. 2010). The first three obviousness factors cited above comprise the prima facie case. *Winner Int'l Royalty Corp. v. Wang*, 202 F.3d 1340, 1350 (Fed. Cir. 2000).

39. The claimed invention must be viewed "'in the state of the art that existed at the time'" the invention was made. *Uniroyal, Inc. v. Rudkin-Wiley Corp.*, 837 F.2d 1044, 1050-51 (Fed. Cir. 1988) (quoting *Interconnect Planning Corp. v. Feil*, 774 F.2d 1132, 1138 (Fed. Cir.1985)).

40. What a reference teaches is a question of fact addressed to a "person of ordinary skill in the art." *In re Bell*, 991 F.2d 781, 784 (Fed. Cir. 1993). The person of ordinary skill is an objective legal construct who is presumed to be aware of all the relevant prior art "and the then-accepted wisdom in the field." *In re Kotzab*, 217 F.3d 1365, 1369 (Fed. Cir. 2000); *Custom Accessories, Inc. v. Jeffrey-Allan Indus., Inc.*, 807 F.2d 955, 963 (Fed. Cir. 1986). This person is not deemed to be an innovator; rather, he is "presumed to be one who thinks along the lines of conventional wisdom in the art." *Standard Oil Co. v. Am. Cyanamid Co.*, 774 F.2d 448, 454 (Fed. Cir. 1985); *see also Life Techs., Inc. v. Clontech Labs., Inc.*, 224 F.3d 1320, 1325 (Fed. Cir. 2000).

41. A proper obviousness analysis requires the recognition that the prior art, not hindsight knowledge of a patentee's success, must motivate a person skilled in the art to do what the patentee has done. *Yamanouchi Pharm. Co., Ltd. v. Danbury Pharmacal, Inc.*, 231 F.3d 1339, 1343 (Fed. Cir. 2000) (citing *In re Rouffet*, 149

F.3d 1350, 1357-58 (Fed. Cir. 1998)); *Grain Processing Corp. v. Am. Maize-Prods. Co.*, 840 F.2d 902, 907 (Fed. Cir. 1988) ("Care must be taken to avoid hindsight reconstruction by using 'the patent in suit as a guide through the maze of prior art references, combining the right references in the right way so as to achieve the result of the claims in suit.'") (quoting *Orthopedic Equip. Co. v. United States*, 702 F.2d 1005, 1012 (Fed. Cir. 1983)).

42. Where a patent challenger's obviousness case relies upon multiple references, the challenger must prove not only that the prior art as a whole taught or suggested the invention, but also that the POOS would have been "'motivated to combine the teachings of the prior art references to achieve the claimed invention.'" *Procter & Gamble Co. v. Teva Pharm. USA, Inc.*, 566 F.3d 989, 994 (Fed. Cir. 2009) (quoting *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1361 (Fed. Cir. 2007)); *KSR*, 550 U.S. at 417-18; *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1356-57 (Fed. Cir. 2007).

43. Where the prior art "teaches away" from the claimed invention rather than motivating a person of ordinary skill in the art to do what the patentee has done, the claimed invention is non-obvious. *In re Hedges*, 783 F.2d 1038, 1041 (Fed. Cir. 1986); *W.L. Gore & Assocs. v. Garlock, Inc.*, 721 F.2d 1540, 1552-53 (Fed. Cir. 1983). "'A reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was

taken by the applicant.'" *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1327 (Fed. Cir. 2009) (quoting *Ricoh Co., Ltd. v. Quanta Computer Inc.*, 550 F.3d 1325, 1332 (Fed. Cir. 2008)); *see also Crocs, Inc. v. Int'l Trade Comm'n*, 598 F.3d, 1294, 1308-09 (Fed. Cir. 2010) (finding invention non-obvious where "[t]he record shows that the prior art would actually discourage and teach away from the use of foam straps . . . . The prior art depicts foam as unsuitable for straps.").

44. The prior art must also provide a reasonable expectation of success. *Boehringer Ingelheim Vetmedica, Inc. v. Schering-Plough Corp.*, 320 F.3d 1339, 1354 (Fed. Cir. 2003) ("A showing of obviousness requires a motivation or suggestion to combine or modify prior art references, coupled with a reasonable expectation of success."); *In re Dow Chem. Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988). "Obvious to try" is not sufficient. *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1380 (Fed. Cir. 1986).

45. The assessment of obviousness also requires examination of objective evidence of non-obviousness. Such objective evidence, when present, must be considered and includes the extent of commercial success of the patented invention, unexpected properties of the invention compared to the prior art, whether the invention satisfies a long-felt need, whether others have failed to find a solution to the problem plaguing the art, and any copying of the invention by others. *Graham*, 383 U.S. at 17-18; *Ashland Oil, Inc. v. Delta Resins & Refractories, Inc.*, 776 F.2d

281, 291 (Fed. Cir. 1985).

46. Objective evidence is "often [] the most probative and cogent evidence in the record." *Stratoflex*, 713 F.2d at 1538. "It may often establish that an invention appearing to have been obvious in light of the prior art was not. It is to be considered as part of all the evidence, not just when the decisionmaker remains in doubt after reviewing the art." *Id*. at 1538-39.

47. Defendants have the burden of proof with respect to *all* of the obviousness factors, including, where relevant, objective evidence of non-obviousness. Specifically,

> the party asserting invalidity bears the initial burden of establishing a *prima facie* case of obviousness under 35 U.S.C. § 103. Once a *prima facie* case has been established, the burden shifts to the patentee to go forward with rebuttal evidence showing facts supporting nonobviousness. The party asserting invalidity, however, always retains the burden of persuasion on the issue of obviousness until a final judgment is rendered. Each fact forming the factual foundation upon which the court bases its ultimate conclusion regarding the obviousness of the claimed subject matter as a whole must be established by clear and convincing evidence.

Ashland Oil, 776 F.2d at 291-92 (internal citations omitted); *see also Hybritech*, 802 F.2d at 1380 (objective evidence must be considered before a conclusion on obviousness is reached and is not merely "icing on the cake").

48. The weight to which the objective evidence is entitled depends on its nature and its relationship to the merits of the invention. *In re GPAC Inc.*, 57 F.3d 1573, 1580 (Fed. Cir. 1995); *Ashland Oil*, 776 F.2d at 305 n.42.

49. "For objective evidence to be accorded substantial weight, its proponent must

establish a nexus between the evidence and the merits of the claimed invention." *GPAC*, 57 F.3d at 1580.

50. "The term 'nexus' is often used, in this context, to designate a legally and factually sufficient connection between the proven success and the patented invention, such that the objective evidence should be considered in the determination of nonobviousness." *Demaco Corp. v. F. Von Langsdorff Licensing Ltd.*, 851 F.2d 1387, 1392 (Fed. Cir. 1988).

1. The Prima Facie Case

51. Apotex contends that the prior art, including the combined teachings of the Lever '892 patent, the '863 patent, and the Kamei article, would have motivated a person of ordinary skill to arrive at the invention claimed in the '805 patent.

a. There Was No Teaching in the Prior Art of Olopatadine's Effect on Human Conjunctival Mast Cells

52. The concept of mast cell heterogeneity – that mast cells differ between species and between different tissues within a species in their structure, contents, and response to stimuli and chemical compounds – was well established by the mid-1990s. (Yanni Tr. 140:7-11; Kaliner Tr. 480:16-482:8; Bielory Tr. 1136:8-1137:1; Abelson Tr. 1732:18-25; TX 69A; TX 103A; TX 221A; TX 219; *see also supra* Finding of Fact # 61).

53. The POOS would have understood that because of mast cell heterogeneity, a researcher must test a compound on the target tissue in the target species in order

to understand the effect of a compound on particular mast cells. (Abelson Tr. 1732:20-1733:7; Kaliner Tr. 477:22-478:11 ("[Y]ou can't translate mast cell responses from an animal model to a human with any level of certainty whatsoever."). In other words, to have a teaching that a compound would be effective in the human eye, a reference must disclose data reporting testing on the mast cells of the human conjunctiva. (Abelson Tr. 1732:20-1733:7 ("It was very clear, with the work of Irani and Schwartz, that the target for a mast cell stabilizer for the human mast cell in the eye would be a human mast cell from the eye.").

54. Other than the Hamilton and Berdy & Abelson articles, none of the prior art cited in this case tested olopatadine on any tissue in humans. The core references relied upon by Apotex – Kamei, the '863 patent, the Lever '892 patent, the Ohmori declaration, the Ohshima paper, and the Ishii and Ohmori abstracts – contain only data from testing on rats and guinea pigs. Moreover, the list of antihistaminic compounds tested in the Berdy & Abelson article did not include olopatadine. The purpose of the study was to determine an appropriate dose range, and not the compound's mechanism of action. Such data would not be instructive to the POOS looking for a human conjunctival mast cell stabilizer. (Kaliner Tr. 477:22-478:11; *see also supra* Findings of Fact § VI.A.2).

55. Although olopatadine is one of the 16 compounds disclosed in claims 2 and 5 of the Lever '892 patent, the Lever patent mentions mast cell stabilization in the context of treating asthma, not allergic conjunctivitis. (*See supra* Findings of Fact

237, 245-46). Moreover, there is no data to support the assertion that some of the Lever compounds act through mast cell stabilization, and thus, a POOS would regard the assertion regarding mast cell stabilization as speculation. (*See supra* Finding of Fact # 262).

56. As a result, the POOS would not have considered any of the prior art relied upon by Apotex to be instructive as to whether olopatadine was a human conjunctival mast cell stabilizer. None of the prior art references teach that olopatadine would stabilize human conjunctival mast cells to a clinically relevant extent. In fact, none of the prior art relied upon by Apotex shows that olopatadine is a mast cell stabilizer in any species or tissue.

b. The Prior Art as a Whole Taught Away from the Claimed Invention

57. None of the prior art teaches that a composition containing olopatadine could be used in the human eye to treat allergic eye disease by stabilizing human conjunctival mast cells. (*See supra* Findings of Fact § VI.A.2).

58. None of the prior art contains data suggesting or supporting an assertion that olopatadine would function as a mast cell stabilizer in the human eye. (Abelson Tr. 1752:7-17; *see also supra* Findings of Fact § VI.A.2).

59. None of the prior art discussed or tested the use of olopatadine in the human eye for any purpose. (*See supra* Findings of Fact § VI.A.2)

60. None of the prior art discussed or tested the use of olopatadine on human

conjunctival mast cells. (*See supra* Findings of Fact § VI.A.2).

61. None of the prior art demonstrated that olopatadine could stabilize mast cells in any animal or human mast cell population. (*See supra* Findings of Fact § VI.A.2).

62. Given mast cell heterogeneity, even if the prior art had demonstrated stabilization of animal mast cells, that would not have given the POOS a reasonable expectation that olopatadine would stabilize human conjunctival mast cells. (Abelson Tr. 1753:12-1754:4; *see, e.g.*, Kaliner Tr. 607:10-17).

63. Hamilton and Kamei were the closest prior art to the invention of the '805 patent. Hamilton, the only testing of olopatadine in humans in the prior art, (Bielory Tr. 1167:13-17), was tested on the skin. The human skin and the human conjunctiva contain MCTC mast cells, and thus, are more similar than any other animal or tissue tested in the prior art. (Abelson Tr. 1764:20-1765:12; Kaliner Tr. 599:14-23).

64. Kamei described the only testing of olopatadine in an eye (there, a guinea pig eye) in the prior art. (Bielory Tr. 1150:4-7).

65. Both Hamilton and Kamei taught away from the invention of the '805 patent by teaching that olopatadine would not be effective as a mast cell stabilizer in those models. (Abelson Tr. 1783:7-22).

66. The Lever patent is also close prior art, and includes olopatadine, along with potentially millions of such compounds, within its generic formula (formula (I)). (*See supra* Finding of Fact # 233). Olopatadine, however, is not one of the

preferred or most preferred compounds of the invention, is not otherwise described in the patent, and is not disclosed in any of the exemplary formulations. (*See supra* Findings of Fact ## 242-44; *see also* Findings of Fact § VI.A.2.h(3)). Most significantly, column 5's discussion of the compounds having antihistaminic activity references those compounds for the treatment of allergies, including allergic conjunctivitis. (*See supra* Findings of Fact § VI.A.2.h(2)).

67. Considering Hamilton and Kamei in combination with Lever, the POOS would weight their understanding of olopatadine strongly in favor of Hamilton and Kamei because those references both employ olopatadine, unlike Lever, and because of the uses to which olopatadine was put in those references. (Abelson Tr. 1934:3-9). Considering Lever at the same time as Kamei and Hamilton, the POOS would be taught away from the use of olopatadine as a mast cell stabilizer. (Abelson Tr. 1933:13-22).

68. Based upon the teachings of all the prior art, the POOS would not have been motivated to select olopatadine as a mast cell stabilizer. (Abelson Tr. 1784:20-24).

69. The POOS would have no expectation based on the prior art that olopatadine would be successful as a mast cell stabilizer. (Kaliner Tr. 655:12-17). To the contrary, the POOS would be directed away from the use of olopatadine to stabilize mast cells based on the Kamei and Hamilton references. (Abelson Tr. 1783:7-1784:18).

70. Nothing in the prior art disclosed the use of a 0.1% w/v concentration of

olopatadine at all, much less for use in the human eye as a mast cell stabilizer. (*See supra* Findings of Fact § VI.A.2.h(3)).

71. The prior art taken as a whole would not have motivated the POOS to use olopatadine to stabilize human conjunctival mast cells at 0.1% w/v. (Kaliner Tr. 655:6-11).

72. The prior art taken as a whole would not have provided the POOS with a reasonable expectation that olopatadine would successfully stabilize human conjunctival mast cells at a concentration of 0.1% w/v. (Kaliner Tr. 655:12-17).

73. Accordingly, the court finds Apotex has failed to establish a prima facie case of obviousness by clear and convincing evidence.

c. The Differences Between the Claimed Invention and the Prior Art

74. The prior art does not suggest using olopatadine to treat allergic eye disease through mast cell stabilization. (*See* Findings of Fact § VI.A.4.a).

75. The prior art does not teach that olopatadine would be effective as a topical ocular treatment for human use. (*See* Findings of Fact § VI.A.4.b).

2. Objective Evidence of Non-obviousness – The Secondary Considerations

76. Even though Alcon has established its prima facie case, the court is required to examine the objective evidence of non-obviousness in the record. *Graham*, 383 U.S. at 17-18; *Stratoflex*, 713 F.2d at 1538-39. The secondary considerations include long-felt need, failure of others, commercial success, acclaim in the field,

and unexpected results. *Ashland Oil*, 776 F.2d at 291; *Corning Glass Works v. Sumitomo Elec. USA Inc.*, 671 F.Supp. 1369, 1398 (S.D.N.Y. 1987), *aff'd*, 868 F.2d 1251 (Fed. Cir. 1989).

a. Long-Felt Need

77. Evidence of a long-felt but unsolved need in the industry for the solution offered by the patented invention supports a finding that the invention would not have been obvious at the time the invention was made. *Monarch Knitting Mach. Corp. v. Sulzer Morat GmbH*, 139 F.3d 877, 884 (Fed. Cir. 1998); *see also* 35 U.S.C. § 103 ("A patent may not be obtained . . . if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious *at the time the invention was made* to a person of ordinary skill in the art.") (emphasis added).

78. "[L]ong-felt need is analyzed as of the date of an articulated identified [sic] problem and evidence of efforts to solve that problem." *Texas Instruments Inc. v. United States Int'l Trade Comm'n*, 988 F.2d 1165, 1178 (Fed. Cir. 1993).

79. The evidence reflects that by the mid-1990s, there was a long-felt need for an effective mast cell stabilizer for the human eye. (Abelson Tr. 1732:7-17; *see also* Finding of Fact # 288).

80. Although cromolyn was known as a mast cell stabilizer, it had been found to be ineffective in the human eye. (Abelson Tr. 1733:21-1734:8; *see also* Finding of Fact # 289).

81. Since that time (1970s), research companies had been looking for a better mast cell stabilizer than cromolyn, and were spending millions of dollars to find such a compound. (Bielory Tr. 1143:7-1144:9; *see also* Finding of Fact # 290).

82. Patanol® was the first product that was effective as a mast cell stabilizer in the human eye. (Abelson Tr. 1736:14-17; *see also* Finding of Fact # 292).

83. Patanol®, a commercial embodiment of the '805 patent, satisfied a long-felt need by providing proven mast cell stabilization for the human eye, and is highly successful in patients who suffer from allergic conjunctivitis as a result. (Abelson Tr. 1745:9-24).

b. Failure of Others

84. Evidence of failed attempts by others supports a finding that the patented invention would not have been obvious. *Advanced Display Sys., Inc. v. Kent State Univ.*, 212 F.3d 1272, 1285 (Fed. Cir. 2000); *Minn. Mining & Mfg. Co. v. Johnson & Johnson Orthopaedics, Inc.*, 976 F.2d 1559, 1574-75 (Fed. Cir. 1992) (reasoning competitors' failure to develop the patented invention suggested nonobviousness); *Yamanouchi Pharm.*, 21 F.Supp.2d at 374 (stating that the evidence showing that "the pharmaceutical industry at large was attempting to improve upon existing [anti-ulcer drugs] with only a small number of producers coming close to success" supports court's conclusion of nonobviousness).

85. No company had been successful by the mid-1990s in finding an effective human conjunctival mast cell stabilizer. (Abelson Tr. 1736:10-13). The reliance on

animal models had frustrated these companies' research efforts – compounds that appeared to be effective in animal models turned out not to be effective in human models. (TX 219) (Church article); Yanni Tr. 142:23-144:2; *see also supra* Finding of Fact # 291).

86. The court finds that there was a failure of others to find a mast cell stabilizer for use in treating allergic eye disease.

c. Commercial Success

87. Commercial success of an invention is evidence that the invention would not have been obvious. *Goodyear Tire & Rubber Co. v. Ray-O-Vac Co.*, 321 U.S. 275, 279 (1944); *Pro-Mold & Tool Co. v. Great Lakes Plastics, Inc.*, 75 F.3d 1568, 1573-74 (Fed. Cir. 1996).

88. "A nexus between the claimed features of the invention and its commercial success is required." *Brown & Williamson Tobacco Corp. v. Phillip Morris Inc.*, 229 F.3d 1120, 1130 (Fed. Cir. 2000) (citing *J.T. Eaton & Co. v. Atlantic Paste & Glue Co.*, 106 F.3d 1563, 1571 (Fed. Cir. 1997)). "[I]f the marketed product embodies the claimed features, and is coextensive with them, then a nexus is presumed and the burden shifts to the party asserting obviousness to present evidence to rebut the presumed nexus." *Id*. (citing *J.T. Eaton & Co.*, 106 F.3d at 1571).

89. Patanol® is a commercial success. Patanol® earned a market share of approximately 70% market share through 2006. (Warner Tr. 1449:2-16; AA-37; *see also* Finding of Fact # 300).

90. By mid-2007, the ten-year total of Patanol® sales in the United States was nearly $2 billion. (Warner Tr. 1446:23-1447:4; TX 112; AA-36; *see also* Finding of Fact # 304).

91. Patanol® is the market leader of prescription allergy products, and has maintained this dominant position despite the presence of major competitors like Allergan, Bausch & Lomb, Johnson & Johnson, and others. (Warner Tr. 1449:25-1450:17, 1488:5-15; *see also* Finding of Fact # 302).

92. Patanol® achieved this success because of its superior clinical efficacy that is driven by its effect as a mast cell stabilizer in the human eye. (Warner Tr. 1450:18-1451:11; Abelson Tr. 1744:25-1745:24; Kaliner Tr. 555:11-21; *see also* Finding of Fact ## 294-96).

93. The evidence reflects a nexus between the claimed features in the '805 patent and the commercial success of Patanol®.

94. This presumption may be rebutted by evidence of substantial marketing or other promotional activity. *McNeil-PPC, Inc. v. L. Perrigo Co.*, 337 F.3d 1362, 1370 (Fed. Cir. 2003); *Brown & Williamson*, 229 F.3d at 1130; *J.T. Eaton & Co.*, 106 F.3d at 1571.

95. The evidence reflects that from 1997 to 2007, Alcon spent over $200 million in advertising and promotion of Patanol®. (Warner Tr. 1479:19-1480:7, 1482:11-18). There is no evidence in the record of administrative costs associated with these efforts.

96. The court finds that Apotex's evidence of Alcon's advertising and promotional costs does not rebut the nexus between the claimed features of the '805 patent and the commercial success of Patanol®.

d. Industry Acclaim

97. Appreciation of the invention by those of ordinary skill in the art is further evidence that the invention would not have been obvious. *E.g.*, *Vulcan Eng'g Co. v. Fata Aluminum, Inc.*, 278 F.3d 1366, 1373 (Fed. Cir. 2002); *In re Piasecki*, 745 F.2d 1468, 1473-74 (Fed. Cir. 1984); *Jenn-Air Corp. v. Modern Maid Co.*, 499 F.Supp. 320, 326-27 (D. Del. 1980), *aff'd*, 659 F.2d 1068 (3rd Cir. 1981).

98. Patanol® has been subject to wide-spread praise within the industry. Immediately upon its launch, doctors were impressed with its performance and commented on its efficacy. (Warner Tr. 1435:16-1437:24). Patanol® was lauded for quickly achieving a market leader position. (TX 795) ("Alcon's starry-eyed hopes for its chronic conjunctivitis drug Patanol are paying off . . . .").

99. This evidence supports Alcon's argument of nonobviousness.

e. Unexpected Results

100. Unexpected superior properties from an invention support the conclusion that the invention was not obvious to one of ordinary skill in the art. *In re Baxter Travenol Labs.*, 952 F.2d 388, 392 (Fed. Cir. 1991); *In re De Blauwe*, 736 F.2d 699, 705 (Fed. Cir. 1984). As the Federal Circuit has recognized, the reason behind this principle is "'that which would have been surprising to a person of ordinary skill in

a particular art would not have been obvious.'" *In re Mayne*, 104 F.3d 1339, 1343 (Fed. Cir. 1997) (quoting *In re Soni*, 54 F.3d 746, 750 (Fed. Cir. 1995)).

101. In order for a showing of unexpected results to be probative of nonobviousness, such evidence must at least establish: "(1) that there actually is a difference between the results obtained through the claimed invention and those of the closest prior art, and (2) the difference actually obtained would not have been expected by one skilled in the art at the time of the invention." *In re Freeman*, 474 F.2d 1318, 1324 (C.C.P.A. 1973) (internal citations omitted).

102. "[W]hen unexpected results are used as evidence of nonobviousness, the results must be shown to be unexpected compared with the closest prior art." *Baxter Travenol Labs.*, 952 F.2d at 392.

103. Evidence of unexpected results discovered after the patent issues are part of the obviousness inquiry. *See Richardson-Vicks Inc. v. Upjohn Co.*, 122 F.3d 1476, 1482-83 (Fed. Cir. 1997) (finding that the court must consider all evidence of unexpected results, even that which it finds to have been unknown at the time of the invention); *In re Zenitz*, 333 F.2d 924, 927 (C.C.P.A. 1964); *Yamanouchi Pharm.*, 21 F.Supp.2d at 370.

104. Olopatadine has several unexpectedly superior properties. First, olopatadine is unexpectedly effective as a mast cell stabilizer in the human eye. Olopatadine exhibits a therapeutic plateau in dose response studies of mast cell stabilization that would not have been expected in the mid-1990s. (Abelson Tr. 1790:24-

1791:22; Kaliner Tr. 535:16-536:8; *see also supra* Finding of Fact # 308).

105. Second, olopatadine is unexpectedly not biphasic. Other than products containing olopatadine, all products available for the treatment of allergic eye disease that have an antihistaminic effect are biphasic, making ophthalmic solutions containing olopatadine unique in this regard. (Yanni. Tr. 171:10-172:2; Kaliner Tr. 536:3-8, 538:1-539:1; AA-16.01-.02; *see also supra* Finding of Fact #309).

106. As a side note, the products that claim to act through mast cell stabilization, with the exception of olopatadine, lack data showing that they stabilized human conjunctival mast cells. (Kaliner Tr. 540:13-21; *see also supra* Finding of Fact # 317). The pharmacological data on these products was based on animal and non-tissue specific mast cell testing. (Kaliner Tr. 540:13-21).

107. Third, olopatadine is unexpectedly superior to other compounds, including the Wellcome Compounds. (Yanni Tr. 191:17-193:7; 253:21-269:6; Kaliner Tr. 538:3-539:1; Abelson Tr. 1790:24-1791:22; TX 206 at ALP013-120410, 11; AA-16.01; AA-89.02; *see also supra* Finding of Fact # 318).

108. Finally, olopatadine's tremendous clinical success and efficacy could also not have been predicted in the mid-1990s. (Abelson Tr. 1790:24-1791:22; *see also supra* Finding of Fact # 319). As noted many times before, Patanol® treats not only the itching associated with an allergy, but also swelling, irritation, tearing, and redness. (Kaliner Tr. 543:4-10; AA-96.01a-96.05a; TX 703; TX 706A; TX 708; TX 714; TX 715; TX 718; TX 726; TX 732A; TX 735; TX 736; TX 749; TX 792).

Patanol® provides long-lasting effective treatment for patients, and is more comfortable than comparator products. (Kaliner Tr. 543:23-544:9, 544:25-545:5; TX 708). Thus, patients are much more satisified with the clinical results. (Kaliner Tr. 543:4-10). These effects could not have been predicted by the POOS as of 1995, when the human conjunctival mast cell stabilizing properties of olopatadine at 0.1% were unknown. (Abelson Tr. 1752:7-17). They are strong evidence of non-obviousness.

3. Conclusion Regarding Obviousness

109. An analysis under *Graham, supra*, considering the scope and content of the prior art, the level of skill in the art, the differences between the prior art and olopatadine, and the objective evidence of nonobviousness, leads to the conclusion that Apotex has failed to prove by clear and convincing evidence that the subject matter claimed in any of claims 1-8 of the ’805 patent would have been obvious within the meaning of 35 U.S.C. § 103 to a person of ordinary skill in the art as of June 6, 1995, the filing date of the 805 patent.

C. Anticipation

110. Title 35 U.S.C. § 102(b) states that a patentee shall be entitled to a patent unless “the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of the application for a patent in the United States.”

111. A claim not satisfying the novelty condition of patentability, as defined in § 102, is

said to be "anticipated." *In re Omeprazole Patent Lit.*, 483 F.3d at 1377.

112. A printed publication will anticipate a claim under § 102(b) only if "each and every [claim] limitation is found either expressly or inherently in a single prior art reference." *Celeritas Techs., Ltd. v. Rockwell Int'l Corp.*, 150 F.3d 1354, 1361 (Fed. Cir. 1998); *see also Sanofi-Synthelabo v. Apotex, Inc.*, 550 F.3d 1075, 1082 (Fed. Cir. 2008) ("Invalidation on this ground requires that every element and limitation of the claim was previously described in a single prior art reference, either expressly or inherently, so as to place a person of ordinary skill in the possession of the invention."). In other words, a printed publication must include all the "limitations," i.e., defining features of the claim, as those limitations are arranged in the claim. *Net MoneyIn, Inc. v. VeriSign, Inc.*, 545 F.3d 1359, 1369 (Fed. Cir. 2008) ("Because the hallmark of anticipation is prior invention, the prior art reference – in order to anticipate under 35 U.S.C. § 102 – must not only disclose all elements of the claim within the four corners of the document, but must also disclose those elements as 'arranged as in the claim.'" (quoting *Connell v. Sears, Roebuck & Co.*, 722 F.2d 1542, 1548 (Fed. Cir. 1983)); *Finisar Corp. v. DirecTV Group, Inc.*, 523 F.3d 1323, 1334 (Fed. Cir. 2008). Simply locating in a prior art reference some mention, in isolation, of each disparate element in a patent's claims is not sufficient to prove anticipation. *See Finisar*, 523 F.3d at 1338. Rather, the descriptions of a claim's elements in a prior art reference must be connected to one another in the same way as the elements are connected in the

claim, such that the prior art actually describes the invention in the claim. *Net MoneyIn*, 545 F.3d at 1369-71; *Finisar*, 523 F.3d at 1338; *Akzo N.V. v. U.S. Int'l Trade Comm'n*, 808 F.2d 1471, 1480 (Fed. Cir. 1986); *Structural Rubber Prods. v. Park Rubber Co.*, 749 F.2d 707, 715-16 (Fed. Cir. 1984) (explaining that "[t]he statutory language mandates" a description not only of every element of a patent claim in a single prior art reference, but also that the elements be arranged as in the claim, since "[s]ection 102 speaks in terms of the invention having been known or used by others, or patented or described in a printed publication").

113. If a claim limitation is not found expressly in a prior art reference, the court may inquire as to whether the missing descriptive matter is necessarily inherent in the thing described in the reference. *Cont'l Can Co. USA v. Monsanto*, 948 F.2d 1264, 1268-69 (Fed. Cir. 1991). Although extrinsic evidence may be referred to "to explain the disclosure of a reference," the Federal Circuit has stated that "[t]he role of extrinsic evidence is to educate the decision-maker to what the reference meant to persons of ordinary skill in the field of the invention, not to fill gaps in the reference." *Scripps Clinic & Research Found. v. Genentech, Inc.*, 927 F.2d 1565, 1576 (Fed. Cir. 1991), *overruled on other grounds by Abbott Labs v. Sandoz, Inc.*, 566 F.3d 1282 (Fed. Cir. 2009); *see also Structural Rubber Prods.*, 749 F.2d at 716 (rejecting argument that "missing elements may be supplied by the knowledge of one skilled in the art or the disclosure of another reference").

114. Inherent anticipation "may not be established by probabilities or possibilities. The

mere fact that a certain thing may result from a given set of circumstances is not sufficient." *Cont'l Can*, 948 F.2d at 1269 (quoting *In re Oelrich*, 666 F.2d 578, 581 (C.C.P.A. 1981)). To be inherent, an undisclosed feature must necessarily and inevitably flow from practice of what is disclosed. *Id.*

115. The question of whether a printed publication includes all of the claim limitations, expressly or inherently, is a question of fact. *Minn. Mining & Mfg. Co. v. Chemque, Inc.*, 303 F.3d 1294, 1301 (Fed. Cir. 2002); *In re Schreiber*, 128 F.3d 1473, 1477 (Fed. Cir. 1997).

1. The Lever Patent Does Not Expressly Anticipate Claims 1-8 of the '805 Patent

116. Apotex contends that the Lever patent, which issued in 1990, disclosed each and every limitation of claims 1-8 of the '805 patent more than one year prior to June 1995.

a. Lever Does Not Disclose Every Species Within a Genus

117. Apotex first contends that claims 2 and 5 of Lever disclose a small genus of compounds, which includes olopatadine, to treat asthma and allergy. Citing *Bristol-Myers Squibb Co. v. Ben Venue Labs., Inc.*, 246 F.3d 1368 (Fed. Cir. 2001), Apotex posits that "[t]his small genus of compounds discloses olopatadine just as if it had been specifically named." (Docket # 318, Apotex, Inc.'s and Apotex Corp.'s Proposed Findings of Fact and Conclusions of Law at 60, Finding of Fact # 250).

118. Disclosure of a genus of chemical compounds generally does not anticipate a claim to a particular species within that genus, because picking and choosing from among the possible options is required to arrive at each species in the genus. 1 Donald S. Chisum, *Patents* § 3.029209b0 (2003) ("This suggests that a prior genus which does not explicitly disclose a species does not anticipate a later claim to that species."); *see also Atofina v. Great Lakes Chemical Corp.*, 441 F.3d 991, 999 (Fed. Cir. 2006) ("It is well established that the disclosure of a genus in the prior art is not necessarily a disclosure of every species that is a member of that genus.").

119. A narrow exception to this general rule was first articulated in *In re Petering*, 301 F.2d 676 (C.C.P.A. 1962), which is cited by the *Bristol-Myers* Court.

120. In *Petering*, the Court affirmed the rejection of a claim to a specific compound, 6, 7-dimethyl-9-[β-monohydroxyethyl]-isoalloxazine. In addition to finding that the prior art reference, known as the Karrer patent, disclosed a generic disclosure of isoalloxazine derivatives, the Court also found the Karrer patent disclosed "certain specific preferences . . . through [a] series of preferred R groups and [its] eight specific isoalloxazines." *Id*. at 681. The Court found that

> the pattern of Karrer's specific preferences [for the six variable substituents on the generic formula] in connection with his generic formula constitutes a description of a definite and limited class of compounds which may be defined with reference to the Karrer generic formula as follows: where X, P and R' are hydrogen, where Y and Z may be hydrogen or methyl, and where R is a member selected from the group

consisting of $-CH_2OH$, $-CH_2CH(OH)CH_2OH$, $-CH_2CH_2OH$, $-CH_2(CHOH)_3CH_2OH$ and $-CH_2(CHOH)_4CH_2OH$.

Id.

The Court explained that the "pattern of preferences" permitted only a "limited number of variations for R, only two alternatives for Y and Z, no alternatives for the other ring positions, and a large unchanging structural nucleus." *Id*. at 681-682. The Court therefore held that "Karrer described to one skilled in the art a limited class of some 20 compounds, including 6, 7-dimethyl-9-[β-monohydroxyethyl]-isoalloxazine, 'as fully as if he had drawn each structural formula or had written each name.'" *In re Schaumann*, 572 F.2d 312, 315 (C.C.P.A. 1978) (quoting *Petering*, 301 F.2d at 682).

121. In *Schaumann*, *supra*, the Court found the invention anticipated where claim 1 of the reference patent contained a formula describing a narrow subset of the disclosed compounds with only one variable denominated "R" and further specifying that "R" was a "lower alkyl" group. 572 F.2d at 316. The patent text defined the R as including seven specific lower alkyl groups, rendering all seven anticipated. *Id*. at 314, 316-17. The *Schaumann* Court, relying almost exclusively on *Petering*, held that the printed publication "embraces a very limited number of compounds closely related to one another in structure," therefore "we are led inevitably to the conclusion that the reference provides a description of those compounds just as surely as if they were identified in the reference by name." *Id.*

at 316-17.

122. Thus, in both *Schaumann* and *Petering*, the prior art "expressly spelled out a definite and limited class of compounds that enabled a person of ordinary skill in the art to at once envisage each member of this limited class." *Eli Lilly & Co. v. Zenith Goldline Pharm., Inc.*, 471 F.3d 1369, 1376 (7th Cir. 2006) (citing *Schaumann*, 572 F.2d at 315; *Petering*, 301 F.2d at 681-82). In other words, the compound was *described* in the prior patent. *See Brown v. 3M*, 265 F.3d 1349, 1351 (Fed. Cir. 2001) (emphasis added) (citing *Titanium Metals Corp. of Am. v. Banner*, 778 F.2d 775, 782 (Fed. Cir. 1985)). As noted by the Federal Circuit:

> The scope of the patent's claims determines what infringes the patent; it is not a measure of what it discloses. A patent discloses only that which it describes, whether specifically or in general terms, so as to convey intelligence to one capable of understanding.

Corning Glass Works v. Sumitomo Elec. U.S.A., Inc., 868 F.2d 1251, 1262 (Fed. Cir. 1989) (quoting *In re Benno*, 768 F.2d 1340, 1346 (Fed. Cir. 1985)).

123. The generic disclosure of Lever would not enable a person of ordinary skill in the art to envision olopatadine. The generic disclosure of Lever encompassed potentially millions of compounds. (Kaliner Tr. 634:8-13; Bielory Tr. 1196:22-1197:14; Abelson Tr. 1775:22-25; *see also supra* Finding of Fact # 233). Although dependent claims 2 and 5 disclose olopatadine as one of possibly 16 compounds, olopatadine is not described as a "preferred" or "most preferred" compound of formula (I), and olopatadine is not referenced in any of the exemplary formulations. (Kaliner Tr. 634:14-23, 638:3-640:15, 656:11-16,

715:19-22; *see also* Findings of Fact ## 237, 242). In fact, olopatadine is not otherwise addressed in the Lever patent, and had not been synthesized as of that date. (Kaliner Tr. 716:3:10; *see also supra* Finding of Fact # 241).

124. The court therefore finds that Apotex has not proven, by clear and convincing evidence, that the Lever patent describes a definite and limited class of compounds such that the person of ordinary skill in the art would envision olopatadine. Accordingly, Apotex's genus/species anticipation argument is rejected. *See Impax Labs., Inc. v. Aventis Pharms. Inc.*, 468 F.3d 1366, 1383 (Fed. Cir. 2006) ("If the members cannot be envisioned, the reference does not disclose the species and the reference is not enabling.").

b. Lever Does Not Teach the Use of Olopatadine as an Ophthalmic Solution for Human Medical Use, and Thus, Does Not Anticipate Claims 1-4 of the '805 Patent

125. Apotex next contends that reading claim 2, in light of the specification and Example 8(I), discloses the use of olopatadine to treat allergic conjunctivitis in humans by way of a topical formulation at 0.1% w/v.

126. As noted above, claim 2 of the Lever patent describes a general chemical formula that includes olopatadine; however, the Lever patent does not disclose olopatadine as one of the "preferred" or "most preferred" compounds of formula (I) in the specification. (*See supra* Finding of Fact ## 237, 242, 324).

127. Olopatadine is not otherwise described in the Lever patent. In fact, olopatadine had not been synthesized at the time. (*See supra* Finding of Fact # 240-41).

128. The Lever patent, at column 5, provides that to the extent the compounds of the invention are mast cell stabilizers, they are effective to treat asthma, not allergic conjunctivitis. (*See supra* Finding of Fact ## 245-46).

129. The ophthalmic formulation disclosed in the Lever patent, exemplified in Example 8(I), uses 0.1% w/v of the active compound, i.e., Compound 1. Compound 1 is not olopatadine. (*See supra* Finding of Fact ## 251, 254-55).

130. Moreover, the Lever patent provides that the amount of active compound (i.e., a compound of formula (I)) will vary with the compound chosen, the route of administration, and the overall health of the mammal. Thus, the person of ordinary skill in the art would not envision using olopatadine at 0.1% w/v, as exemplified in that example, in the human eye. (*See supra* Finding of Fact # 256).

c. The Lever Patent Does Not Anticipate Claims 5-8 of the '805 Patent

131. Claim 5 of the '805 patent claims the method of claim 1 to compositions in which the active compound is the "Z isomer" "substantially free of" the "E isomer." (*See supra* Finding of Fact # 146).

132. The Lever patent does not describe the use of olopatadine, nor the use of the Z isomer free of the E isomer of olopatadine, to a particular level of purity. (*See supra* Findings of Fact § VI.A.2.h(1)).

133. Claims 6-8 of the '805 patent, like claims 2-4, specify particular concentrations of olopatadine. (*See supra* Finding of Fact # 147). For the reasons set forth above,

olopatadine is not embraced within those claims.

134. The court therefore finds that Apotex has failed to prove, by clear and convincing evidence, that the Lever patent anticipates claims 1-8 of the ‘805 patent.

2. The Lever Patent Does Not Inherently Disclose Mast Cell Stabilization

135. Finally, Apotex contends that mast cell stabilization is inherently disclosed in the Lever patent. More specifically, Apotex contends that every time a 0.1% w/v olopatadine ophthalmic solution as disclosed in Example 8(I) is applied to the human eye as taught by the Lever Patent, mast cell stabilization occurs to a clinically relevant extent.

136. Olopatadine stabilizes mast cells in the human eye at 0.1% w/v. (Docket # 173, Stipulation ¶ 10; Kaliner Tr. 683:15-23; *see supra* Finding of Fact # 337).

137. Olopatadine does not stabilize conjunctival mast cells to a clinically relevant extent at all concentrations. (Kaliner Tr. 756:23-757:1) (testifying that olopatadine at 0.001% would not stabilize conjunctival mast cells); *see also supra* Finding of Fact # 338).

138. Compositions containing olopatadine at concentrations that do not stabilize conjunctival mast cells to a clinically relevant extent do not satisfy the limitation of claim 1 of the ‘805 patent. Use of those concentrations would also not fall within any of the dependent claims of the ‘805 patent for the same reason. (Kaliner Tr. 757:2-4; *see Curtiss-Wright Flow Control Corp. v. Velan, Inc.*, 438

F.3d 1374, 1380 (Fed. Cir. 2006) (explaining that dependent claims include all the limitations of the independent claim from which they depend).

139. Thus, in conjunction with the findings listed above, there is no disclosure in the Lever patent, the practice of which would necessarily result in the stabilization of human conjunctival mast cells to an extent that is clinically relevant to the treatment of allergic eye disease through topical administration of olopatadine, or olopatadine substantially free of the E isomer.

140. The court therefore finds that Apotex has failed to prove, by clear and convincing evidence, that the Lever patent discloses that the use of a 0.1% w/v olopatadine ophthalmic solution as disclosed in Example 8(I), applied to the human eye, results in mast cell stabilization to a clinically relevant extent.

3. Conclusion Regarding Anticipation

141. The court finds that Apotex has failed to prove, by clear and convincing evidence, that the Lever patent anticipates the ‘805 patent, either expressly or inherently.

C. Inequitable Conduct

142. “Patent applicants are required to prosecute patent applications with candor, good faith, and honesty.” *Semiconductor Energy Lab. Co., Ltd. v. Samsung Elecs. Co., Ltd.*, 204 F.3d 1368, 1373 (Fed. Cir. 2000) (citing *Molins PLC v. Textron, Inc.*, 48 F.3d 1172, 1178 (Fed. Cir. 1995)).

143. Attorneys, agents, and applicants who have applications pending before the PTO have an uncompromising duty to report all facts concerning possible fraud or

inequitable conduct underlying the application. *See Precision Instrument Mfg. Co. v. Auto. Maint. Mach. Co.*, 324 U.S. 806, 818 (1945); *see also* 37 C.F.R. § 1.56(c) (2010) (stating that the duty of candor extends to "(1) [e]ach inventor named in the application; (2) [e]ach attorney or agent who prepares or prosecutes the application; and (3) [e]very other person who is substantively involved in the preparation or prosecution of the application and who is associated with the inventor, with the assignee or with anyone to whom there is an obligation to assign the application.").

144. If a patent applicant violates these duties, the patent may be held unenforceable due to inequitable conduct. *See Bristol-Myers Squibb Co. v. Rhone-Poulenc Rorer, Inc.*, 326 F.3d 1226, 1233 (Fed. Cir. 2003).

145. "Inequitable conduct includes affirmative misrepresentations of material fact, failure to disclose material information, or submission of false material information, coupled with an intent to deceive." *Novo Nordisk Pharms., Inc. v. Bio-Tech. Gen. Corp.*, 424 F.3d 1347, 1359 (Fed. Cir. 2005) (internal quotation marks and citations omitted).

146. The duty of candor extends throughout the patent's entire prosecution history. *Fox Indus. v. Structural Preservation Sys., Inc.*, 922 F.2d 801, 803 (Fed. Cir. 1990).

147. To prevail, the defendants must prove these elements by clear and convincing evidence. *Star Scientific, Inc. v. R.J. Reynolds Tobacco Co.*, 537 F.3d 1357, 1365 (Fed. Cir. 2008).

148. "Inequitable conduct entails a two-step analysis: first, a determination of whether the withheld reference meets a threshold level of materiality and intent to mislead, and second, a weighing of the materiality and intent in light of all the circumstances to determine whether the applicant's conduct is so culpable that the patent should be unenforceable." *GFI, Inc. v. Franklin Corp.*, 265 F.3d 1268, 1273 (Fed. Cir. 2001) (citing *Baxter Int'l, Inc. v. McGaw, Inc.*, 149 F.3d 1321, 1327 (Fed. Cir. 1998)).

149. Thus, to prevail on their inequitable conduct allegations, Apotex must prove that the prior art or other information that has allegedly been withheld or misrepresented was material to patentability. Apotex must then demonstrate knowledge, chargeable to those responsible for prosecuting the application, of that information and of its materiality. Finally, Apotex must prove that an individual (not "Alcon" generally), having a duty of disclosure to the PTO, intentionally withheld or misrepresented the information with an intent to mislead the PTO. *FMC Corp. v. Manitowoc Co., Inc.*, 835 F.2d 1411, 1415 (Fed. Cir. 1987).

150. A prior art reference or other information is "material" if a reasonable patent examiner would have considered such information important in deciding whether to allow the patent application. *Digital Control, Inc. v. Charles Mach. Works*, 437 F.3d 1309, 1314-16 (Fed. Cir. 2006).

151. A patentee has no duty to disclose "an otherwise material reference if the reference is cumulative or less material than those already before the examiner."

Halliburton Co. v. Schlumberger Tech. Corp., 925 F.2d 1435, 1440 (Fed. Cir. 1991). A reference is said to be cumulative if it "teaches no more than what a reasonable examiner would consider to be taught by the prior art already before the PTO." *Regents of the Univ. of Cal. v. Eli Lilly & Co.*, 119 F.3d 1559, 1575 (Fed. Cir. 1997).

152. Patent examiners are "deemed to have experience in the field of the invention" and are presumed to have acted from the viewpoint of the person of ordinary skill in the art to which the invention pertains. *See In re Lee*, 277 F.3d 1338, 1345 (Fed. Cir. 2002).

153. Intent is a "separate and essential component of inequitable conduct." *Purdue Pharma L.P. v. Endo Pharms. Inc.*, 438 F.3d 1123, 1134 (Fed. Cir. 2006) (internal quotation marks and citations omitted).

154. "[A] finding that particular conduct amounts to 'gross negligence' does not of itself justify an inference of intent to deceive; the involved conduct, viewed in light of all the evidence, including evidence indicative of good faith, must indicate sufficient culpability to require a finding of intent to deceive." *Kingsdown Med. Consultants, Ltd. v. Hollister Inc.*, 863 F.2d 867, 876 (Fed. Cir. 1988).

155. Because evidence of intent to deceive is rarely available, such intent can be inferred from the facts and circumstances surrounding the conduct at issue. *Star Scientific*, 537 F.3d at 1366 (citing *Cargill, Inc. v. Canbra Foods, Ltd.*, 476 F.3d 1359, 1364 (Fed. Cir. 2007)).

156. For cases involving alleged inequitable conduct based on the omission of a material reference, there must be "'clear and convincing evidence that the applicant made a deliberate decision to withhold a known material reference.'" *Star Scientific*, 537 F.3d at 1366 (quoting *Molins*, 48 F.3d at 1181).

157. "Intent to deceive . . . cannot be inferred solely from the fact that information was not disclosed; there must be a factual basis for a finding of deceptive intent." *Purdue Pharma*, 438 F.3d at 1134 (internal quotation marks and citation omitted).

158. If the applicant had no knowledge of the existence of prior art or information, the applicant could not have intended to deceive the examiner by not disclosing it. *FMC Corp.*, 835 F.2d at 1415.

159. Further, the duty to disclose material information applies only to information known "at the time" of the patent prosecution. *Nat'l Bus. Sys., Inc. v. AM Int'l, Inc.*, 743 F.2d 1227, 1239 (Fed. Cir. 1984).

1. The Wellcome HCMC Data in the Kyowa Report Was Not Material

160. Apotex contends that the Kyowa Report was material to patentability, that Dr. Yanni and Mr. Ryan were aware of its materiality and intentionally selected only portions of the Wellcome Compound test data disclosed in the Kyowa Report which supported patentability, while failing to disclose data which did not support patentability. The court will begin its discussion with the first element of an inequitable conduct claim – *i.e.*, the materiality of the Wellcome HCMC test data.

a. The Wellcome HCMC Test Results Were Not Material to Patentability

161. As previously noted, the examiner rejected the claims in both the '227 and '729 applications on grounds of obviousness in light of the Lever patents (which disclosed the Wellcome Compounds). To overcome the examiner's rejection, Dr. Yanni and Mr. Ryan had to demonstrate that olopatadine was unexpectedly superior to the closest prior art compounds. *See Baxter Travenol Labs*, 952 F.2d at 392 ("[W]hen unexpected results are used as evidence of nonobviousness, the results must be shown to be unexpected compared with the closest prior art."). They did this by twice testing the closest prior art compounds – the E-isomer and Wellcome Compounds I and II – in a PARC assay and an *in vitro* HCMC assay. (TX 6; TX 105 at KYP004-00413-14; *see also* Smith Tr. 1307:6-1308:2).

162. Apotex contends that because the applicants represented the importance of showing mast cell stabilizing activity in human conjunctival mast cells, the Wellcome HCMC test results – the only tests performed on the human conjunctiva – were material to patentability.

163. Dr. Yanni tested the Z and E isomers of olopatadine and the Wellcome Compounds twice in February 1994. (*See supra* Finding of Fact ## 344, 346).

164. Dr. Yanni concluded that the data from the tests was inconclusive, but, based upon his experience testing antihistaminic compounds, determined that the combined data from the two tests reflected that the Wellcome Compounds were likely

biphasic. He came to this conclusion by inserting the test data on to a graph, and noting its curvature. (*See supra* Finding of Fact ## 345-47).

165. Dr. Yanni's conclusion that the Wellcome Compounds were biphasic was reasonable, and given the later testing of the Wellcome Compounds in 2008, Dr. Yanni's interpretation was, in fact, correct. (*See supra* Finding of Fact # 348).

166. Moreover, on a more practical level, Mr. Killworth, Alcon's expert in patent practice and procedure, testified that it would have been improper to submit such inconclusive data to the patent examiner. (Killworth Tr. 1966:10-1967:9, 1973:4-12).

167. The court therefore finds that the Wellcome Compound HCMC test data was not material to patentability.

b. The Inclusion of Table 3 (the PARC Test Data) to the Exclusion of the Wellcome HCMC Data Was Not Inconsistent

168. Apotex next contends that the Wellcome HCMC test results were also material because they were inconsistent with Mr. Ryan's representations that olopatadine is a superior mast cell stabilizer *compared* with the Wellcome Compounds of the Lever patent.

169. Table 3's PARC test results were not inconsistent with the Wellcome HCMC test results because the claims of the '729 application, as originally filed, were not limited to humans or mast cell stabilization. (*See supra* Finding of Fact # 353).

170. Thus, the PARC test data was sufficient to show the superior anti-allergic activity

of olopatadine as compared to the Wellcome Compounds. (*See supra* Finding of Fact # 354).

171. Mr. Ryan prepared the 1996 Amendment to the '729 application, and amended claim 1 to add the limitations "in humans" and comprising "stabilizing conjunctival mast cells." (TX 4 at ALP001-042089; Ryan Tr. 1609:1-8).

172. Mr. Ryan presented argument to the PTO. The argument at issue in this case is located in paragraph (iv) of the 1996 Amendment, and reads:

> Lastly, even ignoring (i) - (iii) above, there is no way to predict, given the disclosures of Kamei et al. and Lever, that the compounds recited in Applicants' Claims would possess significantly superior conjunctival mast cell stabilization activity compared to the structurally similar compounds exemplified by Lever. In this regard, Applicants direct the Examiner's attention to Table 3 found on page 10 of Applications' Specification. This Table illustrates the statistically significant superior mast cell stabilization activity that the Z- and E-isomers of the 2-acetic acid derivative have compared to the 2-carboxylic acid and 2-acrylic acid derivatives exemplified by Lever. Thus, a combination of Lever and Kamei et al. in no way discloses or suggests the method recited in Applicants' amended Claims.

(TX 4 at ALP001-042094).

173. Stated differently, Mr. Ryan was arguing that if one ignored the concept of mast cell heterogeneity, (and assume that animal test results are equivalent to human test results), then the data showed that olopatadine was a superior human conjunctival mast cell stabilizer to the Wellcome Compounds. (*See supra* Finding of Fact # 357).

174. In light of all the other data in the specification of the ‘805 patent, the POOS, considering the data in Table 3, and ignoring mast cell heterogeneity, would conclude that the superior anti-allergic effect of olopatadine shown in Table 3 is a result of its superior human conjunctival mast cell stabilizing activity. (*See supra* Finding of Fact # 358).

175. Subsequent testing of the Wellcome Compounds in 2008 confirmed that the Wellcome Compounds are indeed biphasic, and thus, not superior mast cell stabilizers to olopatadine. (Miller Tr. 1510:5-1512:7, 1512:8-1525:1; *see also supra* Findings of Fact ## 359-60).

176. In any event, MPEP 716.01(c) requires that an assertion regarding unexpected results be supported by an appropriate affidavit or declaration. (*See supra* Finding of Fact # 363).

177. The argument presented in paragraph (iv) is an argument for unexpected results. (Smith Tr. 1336:8-10). The data was not supported by a declaration signed by the inventors, as required by the MPEP, and the examiner did not ask for a declaration. Because the examiner did not ask for a declaration, one may reasonably conclude that the examiner did not rely on that statement. (*See supra* Finding of Fact # 364).

178. The court finds that Apotex has failed to prove, by clear and convincing evidence, that the Wellcome HCMC data was material to patentability.

2. Dr. Yanni and Mr. Ryan Did Not Withhold the Wellcome HCMC Data With Deceptive Intent

a. Dr. Yanni and Mr. Ryan Reasonably Believed that the Wellcome HCMC Data Showed that Olopatadine Was Superior to the Wellcome Compounds

179. Apotex contends that Dr. Yanni and Mr. Ryan were aware of the Wellcome HCMC data in the Kyowa Report, were aware that the Wellcome HCMC data was specifically created to argue patentability, and were aware that the data was adverse to patentability. Thus, contends Apotex, Dr. Yanni and Mr. Ryan deliberately withheld the Wellcome HCMC data from the PTO.

180. The Wellcome HCMC data was not adverse to Alcon's patent position. As noted numerous times in this order, Dr. Yanni reasonably concluded that the Wellcome HCMC test results showed that the Wellcome Compounds were biphasic, and Mr. Ryan understood this fact to be true. (*See supra* Finding of Fact ## 115, 347-48, 368).

181. Dr. Yanni's and Mr. Ryan's beliefs are supported by Dr. Adamski's letter to Kyowa, which reports that there is a significant difference in activity between olopatadine and the Wellcome Compounds. (*See supra* Finding of Fact # 369).

182. In addition, Dr. Yanni checked "no further interest" in the compound status reports for the Wellcome Compounds. (*See supra* Finding of Fact ## 117, 371).

b. Dr. Yanni and Mr. Ryan Did Not Selectively Disclose the PARC test and Withhold the Wellcome HCMC Test Results With an Intent to Deceive

183. Dr. Yanni and Mr. Ryan did not selectively disclose only the PARC test data (Table 3) and selectively exclude the Wellcome HCMC test data (Figure 1 of the Kyowa Report), with an intent to deceive.

184. Dr. Yanni gave Mr. Ryan a copy of the Kyowa Report with circles around the written description of the PARC test and data for the PARC test (Table 3). (*See supra* Finding of Fact # 372).

185. Mr. Ryan included the information in the abandoned draft CIP. Mr. Ryan only reviewed the information that he was directed to by Dr. Yanni for the purpose of preparing the draft CIP. (*See supra* Finding of Fact # 374).

186. Mr. Ryan included the same information in the '729 application. (*See supra* Finding of Fact # 375). In drafting the '729 application, he did not review the Kyowa Report. In fact, the Kyowa Report was not in his file for the '805 patent; it was found in his file for the abandoned CIP application. (*See supra* Finding of Fact # 376).

187. Mr. Ryan did not deliberately withhold Figure 1 of the Kyowa Report, reflecting the Wellcome HCMC test data, with an intent to deceive. (*See supra* Finding of Fact # 378).

188. Dr. Yanni likewise did not selectively disclose Figure 1 to the exclusion of Table 3. (*See supra* Finding of Fact # 379).

189. Dr. Yanni believed, based upon his vast experience testing antihistaminic compounds, that the Wellcome Compound test data was inconclusive, and that the

slope of the Wellcome Compound test data as shown in Figure 1 reflected a biphasic curve. (*See supra* Finding of Fact # 115, 347-48).

c. The Totality of Circumstances Do Not Warrant a Finding of Deceptive Intent

190. The totality of the circumstances does not warrant a finding of deceptive intent on the part of Dr. Yanni or Mr. Ryan.

(1) The Deleted Sentence From the Kyowa Report Does Not Warrant a Finding of Deceptive Intent

191. The portion of the Kyowa Report that was located in Mr. Ryan's file for the '227 CIP application contained an additional sentence: "These data do not provide a basis for circumventing the Wellcome patent covering the anti-allergic utility of KW-4679 and related compounds." (TX 794; *see supra* Finding of Fact # 391).

192. There is no evidence that this sentence was removed from the copy given to Apotex with deceptive intent. In fact, the evidence reflects that Dr. Yanni does not know how the sentence was removed. (*See supra* Finding of Fact # 392).

193. Moreover, the sentence does not show that the Wellcome Compounds were superior to olopatadine. Rather, the sentence reflects the fact that the data did not support an inference that olopatadine was superior to the E isomer, which was within the scope of the Lever patent. (*See supra* Finding of Fact # 393).

(2) The Statement Made in Dr. Yanni's 2007 Patent Application Does Not Show Deceptive Intent

194. Dr. Yanni's '041 patent application relates primarily to the treatment and

prevention of ocular and dermal wounds. (Yanni Tr. 328:5-14, 402:22-404:14).

195. The patent application provides that one of the embodiments of the invention is for the treatment and prevention of conjunctival disease, such as allergic conjunctivitis. (TX 524 at AI009826; *see also supra* Finding of Fact # 398).

196. The '041 patent application listed the Wellcome Compounds by chemical name as mast cell stabilizers in a list of compounds – a list that spans four full columns of the patent. (TX 524 at AI009826-28; *see also supra* Finding of Fact # 399).

197. The '041 patent application also names the Lever patent numbers ('865 and '892) and incorporates them by reference into the patent. (TX 524 at AI009828).

198. Although the patent application referenced the Lever patents by patent number and the Wellcome Compounds by chemical name, Dr. Yanni testified that he did not draft the '041 patent application, and did not recognize, when he reviewed the patent application, the chemical name of the Wellcome compounds nor the patent numbers of the Lever patents. (*See supra* Finding of Fact # 400-01).

199. Mr. Ryan testified that he did not draft the '041 patent application, and instead, employed an outside law firm for that task. (*See supra* Finding of Fact # 402).

200. Mr. Ryan did briefly review the '041 patent application for completeness prior to filing it with the PTO, but does not remember noticing the reference to the Lever patents or to the Wellcome Compounds. (*See supra* Finding of Fact # 403).

201. Dr. Yanni's and Mr. Ryan's explanations are reasonable, and do not reflect deceptive intent.

(3) Mr. Ryan's Failure to Disclose the '227 CIP Application Is Not Evidence of an Intent to Deceive

202. Mr. Ryan failed to disclose the abandoned '227 CIP application to the PTO. (*See supra* Finding of Fact # 382).

203. The failure to disclose the '227 application is not evidence of an intent to deceive. In the mid-1990s, the practice was not to disclose rejections in earlier related prosecutions; rather, practitioners would ensure that all of the related prior art was brought before the examiner, as Mr. Ryan did here. (*See supra* Finding of Fact # 385).

204. Moreover, as of 1995, the Federal Circuit had never held that the failure to disclose an abandoned application was evidence of an intent to deceive. (*See supra* Finding of Fact # 384).

(4) The Repeated Failure to Include the Wellcome HCMC Test Data Is Not Evidence of an Intent to Deceive

205. The failure to disclose the Wellcome HCMC test data was not material to patentability for the reasons discussed numerous times, and thus, was not evidence of an intent to deceive.

3. Conclusion Regarding Inequitable Conduct

206. Apotex has failed to prove, by clear and convincing evidence, that Dr. Yanni and Mr. Ryan evidenced an intent to deceive. The totality of the evidence in this case demonstrates that Apotex has not proven, by clear and convincing evidence, that

the ’805 patent is unenforceable due to the inequitable conduct on the part of Dr. Yanni or Mr. Ryan.

207. Even if the court had determined that Apotex had met their burdens of proof on the elements of materiality and intent for any of their arguments, the court is vested with the discretion to balance the degree of materiality and degree of intent to make an equitable judgment as to whether the conduct was so culpable that the patent should be barred from enforcement. *Life Techs., Inc. v. Clontech Labs., Inc.*, 224 F.3d 1320, 1324 (Fed. Cir. 2000).

208. Here, even if Apotex had proven the required elements, the degree of culpability of Dr. Yanni and Mr. Ryan would be slight, and thus not sufficient to convince this court that the proper remedy would be to invalidate the ’805 patent.

209. The totality of the evidence in this case demonstrates that Apotex has not proven, by clear and convincing evidence, that the ‘805 patent is unenforceable due to inequitable conduct on the part of Dr. Yanni and Mr. Ryan.

D. Written Description

210. Apotex contends that the ‘805 patent does not demonstrate to one of ordinary skill in the art that the inventors had possession of the invention as of June 1995.

211. The specification of a patent must “contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set

forth the best mode contemplated by the inventor of carrying out his invention." 35 U.S.C. § 112, ¶ 1.

212. To satisfy the written description requirement, the description in a patent must "'clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed.'" *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (en banc) (alteration in original) (quoting *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1562-63 (Fed. Cir. 1991)). "In other words, the test for sufficiency is whether the disclosure of the application relied upon reasonably conveys to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date." *Id*. (citing *Vas-Cath*, 935 F.2d at 1563). While "possession" is not the clearest term, "the hallmark of written description is disclosure. Thus, 'possession as shown in the disclosure' is a more complete formulation." *Id*.

213. The written description requirement does not require actual reduction to practice; constructive reduction to practice is sufficient so long as the specification identifies the claimed invention in a definite way. *Id*. at 1352. *See also Falko-Gunter Falkner v. Inglis*, 448 F.3d 1357, 1366 (Fed. Cir. 2006) (emphasis in original) ("[A]n actual reduction to practice is not required for written description."); *Pfaff v. Wells Elecs., Inc.*, 525 U.S. 55, 61 (1998) ("It is well settled that an invention may be patented before it is reduced to practice.").

214. "[A] description that merely renders the invention obvious does not satisfy the

requirement." *Ariad Pharms.*, 598 F.3d at 1352 (citing *Lockwood v. Am. Airlines*, 107 F.3d 1565, 1571-72 (Fed. Cir. 1997)).

215. Whether a patent satisfies the written description requirement is an issue of fact. *Id*. at 1351.

1. Apotex Is Precluded From Raising This Theory Post-Trial

216. Apotex did not disclose any § 112 invalidity theories to Alcon until after the trial of this matter. Moreover, Apotex did not identify any § 112 issue in its trial brief or in its opening statement at trial. (Docket # 174, Apotex's Trial Brief).

217. On May 13, 2010, during a scheduling call with the court regarding post-trial papers, Apotex for the first time revealed that it had a written description invalidity theory. On May 24, 2010, Apotex's counsel sent a letter to Alcon describing this new invalidity theory. (Docket # 317, Ex. D, May 24, 2010 Letter from C. Kuchii to T. Selby). The substance of the three sentence letter was that the asserted claims of the '805 patent are invalid for lack of sufficient written description under the court's claim construction of the term "stabilizing conjunctival mast cells" because "[t]he '805 patent does not contain any clinical data for testing in a living human being." (*Id*.).

218. The court finds that Alcon has been prejudiced by this belated disclosure; Apotex is therefore precluded from asserting this theory of invalidity.

2. Apotex's Written Desciption Theory Fails on the Merits

219. Even if Apotex had notified Alcon of this new invalidity theory pre-trial, the court

finds that Apotex fails to prove, by clear and convincing evidence, that the '805 patent fails the written description requirement of 35 U.S.C. § 112.

220. The court construed the claim "stabilizing conjunctival mast cells" in claim 1 of the '805 patent to mean "preventing or reducing release of mediators including histamine from mast cells in the conjunctival to an extent clinically relevant in the treatment of allergic eye disease."

221. Apotex contends that the '805 patent lacks a sufficient written description because it does not contain any clinical data or the results of testing in living human beings.

222. As noted above, the written description standard does not require actual proof of the invention; it does not require that the invention have been made or used yet. *See, e.g.*, *Ariad Pharms.*, 598 F.3d at 1352 ("We have made clear that the written description requirement does not demand either examples or an actual reduction to practice; a constructive reduction to practice that in a definite way identifies the claimed invention can satisfy the written description requirement.").

223. As quoted at length in the Supreme Court's 1998 *Pfaff* opinion, it has been true since 1888 that "[t]he law does not require that a discoverer or inventor, in order to get a patent for a process, must have succeeded in bringing his art to the highest degree of perfection. It is enough if he describes his method with sufficient clearness and precision to enable those skilled in the matter to understand what the process is, and if he points out some practicable way of putting it into operation." *Pfaff*, 525 U.S. at 62 (quoting *The Telephone Cases*, 126 U.S. 1, 535-36 (1888)).

224. Given the case law that an invention does not actually have to be used, or even made, in order to satisfy the written description requirement, clinical testing cannot be required to satisfy the written description requirement. Nor is clinical data required in related contexts. In the utility context, 35 U.S.C. § 101, the MPEP instructs applicants that clinical data is not required in a patent application. MPEP § 2101.02(d), 6th Ed. (Rev. 2).

225. In *In re '318 Patent Infringement Litig.*, the Federal Circuit held that human clinical data is not required to claim treatment of humans for purposes of meeting the utility requirement of 35 U.S.C. § 101:

> Typically, patent applications claiming new methods of treatment are supported by test results. But it is clear that testing need not be conducted by the inventor. In addition, human trials are not required for a therapeutic invention to be patentable. Our predecessor court, the United States Court of Claims and Patent Appeals, held in *In re Krimmel* that patent applications need not "prove that compounds or other materials which [the applicant] is claiming, and which [the applicant] has stated are useful for 'pharmaceutical applications' are safe, effective, and reliable for use with humans." 292 F.2d 948, 954 (C.C.P.A. 1961). As we observed in *In re Brana*, "[w]ere we to require Phase II testing [human trials] in order to prove utility, the associated costs would prevent many companies from obtaining patent protection on promising new inventions, thereby eliminating an incentive to pursue . . . potential cures." 51 F.3d 1560, 1568 (Fed. Cir. 1995); *see also Scott v. Finney*, 34 F.3d 1058, 1063-64 (Fed. Cir. 1994).

583 F.3d 1317, 1324-25 (Fed. Cir. 2009) (alterations in original). Although the issue before the Federal Circuit was whether the invention met the utility

requirement – i.e., that the patentable invention be useful – the court finds the quoted language highly persuasive. In the opinion, the Federal Circuit likened the utility requirement to the enablement requirement – an inquiry also very similar to that for written description. *See '318 Patent Infringement Litig.*, 583 F.3d at 1324 ("If a patent claim fails to meet the utility requirement because it is not useful or operative, then it also fails to meet the how-to-use aspect of the enablement requirement."); *Ariad Pharms.*, 598 F.3d at 1352 (noting that the "written description and enablement requirement often rise and fall together"). Moreover, the conclusion that human clinical trials are a requirement for a therapeutic invention to be patentable would run counter to the Federal Circuit's stated concern that "the associated costs" of such a requirement "would prevent many companies from obtaining patent protection on promising new inventions, thereby eliminating an incentive to pursue . . . potential cures." *'318 Patent Infringement Litig.*, 583 F.3d at 1324. (alteration in original) (quotation marks omitted).

226. The court therefore rejects Apotex's argument, and finds that the '805 patent reasonably conveys to those skilled in the art that the inventors were in possession of the claimed subject matter as of the filing date. The patent is explicit that the invention relates to the use of olopatadine or the E isomer for the treating and/or preventing allergic eye diseases, such as allergic conjunctivitis. The patent discusses the mechanism of action (mast cell stabilization); describes that the product is for clinical use; and describes the concept of achieving clinically

relevant mast cell stabilization. (*See* Findings of Fact § VI.D.).

227. The court finds that Apotex has failed to prove, by clear and convincing evidence, that the '805 patent fails for lack of a written description under 35 U.S.C. § 112.

IV. Summary of Conclusions

228. The court finds that Plaintiffs have proven, by a preponderance of the evidence, that the Defendants' generic equivalent of Plaintiffs' patented allergy topical ocular medication, Patanol®, infringed claims 1-8 of the '805 patent.

229. The court further finds that Defendants have failed to prove, by clear and convincing evidence, that claims 1-8 of the '805 patent are invalid as anticipated under 35 U.S.C. § 102, as obvious under 35 U.S.C. § 103, and for lack of written description under 35 U.S.C. § 112. The court further finds that Defendants have failed to prove by clear and convincing evidence that the '805 patent is unenforceable due to inequitable conduct.

SO ORDERED this 23rd day of May 2011.

RICHARD L. YOUNG, CHIEF JUDGE
United States District Court
Southern District of Indiana

Electronic Copies to:

Bruce Roger Genderson
WILLIAMS & CONNOLLY LLP
bgenderson@wc.com

Adam L. Perlman
WILLIAMS & CONNOLLY LLP
aperlman@wc.com

Jessamyn S. Berniker
WILLIAMS & CONNOLLY LLP
jberniker@wc.com

Robert B. Breisblatt
KATTEN MUCHIN ROSENMAN LLP.
robert.breisblatt@kattenlaw.com

Craig M. Kuchii
KATTEN MUCHIN ROSENMAN LLP
craig.kuchii@kattenlaw.com

Thomas J. Maas
KATTEN MUCHIN ROSENMAN LLP
thomas.maas@kattenlaw.com

Christopher J. Mandernach
WILLIAMS & CONNOLLY LLP
cmandernach@wc.com

Martin S. Masar III
KATTEN MUCHIN ROSENMAN LLP
martin.masar@kattenlaw.com

Thomas H. L. Selby
WILLIAMS & CONNOLLY LLP
tselby@wc.com

Daniel P. Shanahan
WILLIAMS & CONNOLLY LLP
dshanahan@wc.com

Shelley J. Webb
WILLIAMS & CONNOLLY LLP
swebb@wc.com

Brian J. Sodikoff
KATTEN MUCHIN ROSENMAN LLP
brian.sodikoff@kattenlaw.com

Abram B. Gregory
TAFT STETTINIUS & HOLLISTER LLP
agregory@taftlaw.com

Donald E. Knebel
BARNES & THORNBURG LLP
donald.knebel@btlaw.com

Paul B. Hunt
BARNES & THORNBURG LLP
paul.hunt@btlaw.com

Deborah Pollack-Milgate
BARNES & THORNBURG
dmilgate@btlaw.com

Gayle A. Reindl
TAFT STETTINIUS & HOLLISTER LLP
greindl@taftlaw.com

Todd G. Vare
BARNES & THORNBURG LLP
todd.vare@btlaw.com